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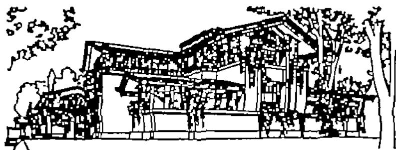
A Primer of

CONGESTIVE HEART FAILURE

by

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DEDICATED

TO

VIVIAN GERARD BURCH

whose unstinted support and interest

have made my work possible

Preface

THIS lecture series on congestive heart failure, one of the most important and most common disease states confronting man, is primarily intended for the medical student, young graduate of medicine, and general practitioner. An attempt has been made to present the material to conform with the tradition of the American Lecture Series. The concepts have been condensed to give the reader the present day ideas on the mechanism and management of congestive heart failure, no attempt having been made to cover every aspect of the subject. Because digitalis and mercurial diuretics are employed so extensively in this disease state, these drugs are discussed in separate chapters, with special emphasis on their practical use. It is hoped that these four chapters will arouse further interest in and assist in the understanding of the mechanism and management of congestive heart failure.

Much of the material in this series has been borrowed freely from articles previously published in collaboration with Dr C. Thorpe Ray. For permission to utilize this material, appreciation is expressed to the editors and publishers of the journals in which these articles have appeared: *American Heart Journal*, Dr Jonathan Meakins and the C. V

Mosby Company *Circulation* Dr Thomas McMillan and Grune and Stratton Inc. and *Medical Clinics of North America* Mr Dwight J Hotchkiss and W B. Saunders Company The excellent editorial assistance of Miss Lois DeBakey who aided in the preparation of these chapters, is gratefully acknowledged.

G. E. B.

Contents

CHAPTER TWO TREATMENT

CHAPTER THREE DIGITALIS

CHAPTER FOUR MERCURIAL DIURETICS

A Primer of

CONGESTIVE HEART FAILURE

(CHAPTER ONE)

Mechanism of Congestive Heart Failure

INTRODUCTION

CONGESTIVE heart failure constitutes one of the enigmas in medicine today (1–7) Its mechanism was considered by most physiologists and clinicians to be clearly understood until recently (8) when the problem was reinvestigated and found to be extremely complex and far from clarified Reconsideration of the pathologic physiology of congestive heart failure has not only added much to our knowledge of cardiac function and hemodynamic states but has also reopened the field of electrolyte and water balance in normal man and in man afflicted with cardiac disease as well as other abnormal states. Renewed interest in disturbances of electrolyte and water balance in congestive heart failure has emphasized the complexity of this problem.

Interestingly enough, the important recent investigations into the mechanism of congestive heart failure have not modified materially if at all, the procedures employed during the last 15 to 20 years in the management of the clinical syndrome. Nevertheless, because of the importance and frequency of occurrence of congestive heart failure in medicine, a brief discussion of certain aspects of its mechanism and management may be of value. Mercurial diuretics and

digitalis will be briefly discussed separately because these drugs enjoy significant roles in the care of patients with congestive heart failure

DEFINITION

For purposes of orientation, these discussions, unless otherwise stated are concerned with the clinical syndrome of *chronic congestive heart failure* This is a syndrome which occurs frequently in man with cardiac disease and which has probably never been adequately produced in the experimental animal.

The syndrome, when fully developed in man, is characterized by dyspnea, generalized edema, which is most severe in the dependent portions of the body generalized and symmetric venous hypertension, diffuse hepatomegaly and possibly peritoneal or pleural transudates or both. Bilateral basal pulmonary râles, accentuated pulmonic second sound pulsus alternans, gallop rhythm, orthopnea weakness and many other manifestations may be present. Although there may be variations in details, all well known to clinicians, the general pattern is consistent (9 10, 11)

Even though the presentation is concerned primarily with chronic congestive heart failure, the concepts may easily be extended to acute congestive failure and other special manifestations and variations of this disease

ASPECTS OF THE MECHANISM OF CONGESTIVE HEART FAILURE

Since the mechanism of chronic congestive heart failure constitutes such a baffling problem, it is not possible to present in a brief discussion the entire scope of the pathologic physiology of congestive failure Therefore, only certain

aspects will be presented to describe the problems encountered, in an attempt to clarify certain phases of thought and to indicate certain established facts and inconsistencies in interpretation. The numerous gaps in current knowledge will become evident from this discussion. Obviously most of these concepts and data are not new but it is likely that some of them have not been considered generally in this fashion. Although Starling clearly presented the problem over 50 years ago (12) little additional information of a fundamental nature has since been added. About 10 years ago Starr and Rawson (4) again lucidly presented certain basic aspects of the hemodynamic principles concerned with congestive heart failure, but these have been disregarded or forgotten by many. The concepts previously described by these investigators, as well as by others, will be reviewed in this presentation.

The complexity of the problem and inability to produce the syndrome in experimental animals have resulted in errors in research and thought, and progress has thus been slow. Most errors have occurred because of variations in the clinical state of the failure under study, inadequacies of the methods employed, complicating clinical states, complicating influences of associated therapeutic procedures, or because the sequelae of failure of the heart were being observed rather than actual failure of the pump itself. These and other factors have created difficulties in integration and comparison of observations, leading to considerable misunderstanding and confusion. Partially because of these factors, no major advance has been made toward solution of this problem.

The clinical manifestations observed at the bedside are mainly sequelae of cardiac disease or failure of the pump. Most observers investigating congestive heart failure have studied these sequelae rather than the heart or pump itself

This is understandable since the pump cannot readily be studied, whereas some aspects of the sequelae are more easily approached

DEFINITIONS OF CLASSICAL CONCEPTS

For purposes of orientation, the two classical concepts of congestive heart failure will be defined briefly:

(1) The backward failure concept (9 10, 11) With failure of a ventricle to pump adequately the blood returning to it accumulates proximally in the atrium and veins. In

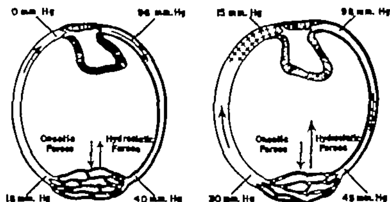


Figure 1. Diagrammatic representation of the classical concept f backward failure. The normal circulatory circuit is shown with normal mean pressures in the circuit and vectors f essentially equal magnitude indicating mean net effective oncotic and hydrostatic forces in the capillary bed. In the circulatory circuit with "backward failure or congestion of blood proximal to the heart, there is an elevation in pressure in the venous system and resultant increase in magnitude f the hydrostatic force, which tends to remove fluid from the vascular system t greater ra than oncotic force, which returns the fluid to the circulation. Because of this, edema develops.

association with this accumulation of blood in the veins venous pressure increases, the venous blood pressure gradient falls, venous stasis occurs and blood accumulates under increased pressure in the small peripheral vessels. The increase in hydrostatic pressure produces a greater loss of fluid and electrolytes into the tissue spaces, resulting in formation of edema. Furthermore with stasis the capillary endothelium becomes anoxic, with resultant increased capillary permeability which tends to enhance formation of edema (Fig. 1) When the capillaries near the peritoneal and pleural surfaces become sufficiently involved transudation

FORWARD FAILURE CONCEPT

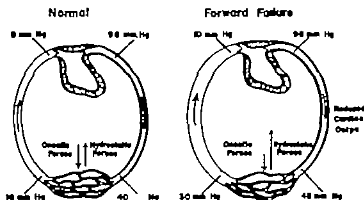


Figure 2. Diagrammatic representation of the classical concept of forward failure. The normal circulatory circuit is compared with that of forward failure. In the latter insufficient blood is forced to the tissues. This is said to result in anoxia and an increase in capillary permeability to blood proteins, which escape into the tissue spaces. This reduces the effective oncotic pressure which returns fluid to the blood vessels. Stasis of blood also occurs in the capillaries, venules and veins because of loss of vis a *tergo* and failure of the failing heart to pump blood forward. Venous pressure is elevated, increasing hydrostatic forces in the capillaries. This produces further loss of fluid into the tissue spaces.

develops and ascitic and pleural fluids accumulate Engorgement of the hepatic veins and sinusoids associated with increased intravascular pressure causes diffuse distention of the liver Changes in renal function and in the urine are considered to be secondary to the venous hypertension and venous stasis with resultant impairment of renal blood flow but until recently no role was attributed to the kidneys in the development of the syndrome of congestive failure.

(2) The forward failure concept (1 9 10, 11) With failure of the heart to pump blood forward, the tissues of the body are deprived of a sufficient quantity of blood anoxia or asphyxia develops, the capillary endothelium increases in permeability the oncotic and hydrostatic forces become unbalanced edema develops and the syndrome is established. There is stasis of blood in the peripheral vessels due to insufficiency of the heart. This increases the anoxia and produces cyanosis. Changes in renal function and urinary constituents are considered to be the result of impaired circulation through the kidneys (Fig 2) but, again, until recently no one attributed any significant role to the kidneys in the development of the clinical syndrome.

CARDIAC EDEMA

In chronic congestive heart failure the fluid compartments of the body are increased especially the intercellular fluid usually including plasma volume The interstitial fluid is *isotonic* it has a *pH* of about 7.4 and has essentially the same *electrolyte content* as normal interstitial fluid The protein content is approximately 0.5 gram per 100 cc Although these values are not considered to be significantly different from normal intercellular fluid, unaltered normal interstitial body fluid has probably never been collected in adequate quantities to be studied The various methods em

ployed to collect interstitial fluid probably injure cells, blood vessels and lymphatic vessels sufficiently to cause an abnormal type of fluid to accumulate. The fluid collected must be an exudate produced by trauma or a foreign body. Theoretic or indirect calculations of the chemical and physical characteristics of normal interstitial fluid are subject to well known errors and are often based upon grossly erroneous assumptions. It is important to realize that the constitutional relationships of edema fluid to normal interstitial fluid are not known precisely and, therefore, any arguments concerning the mechanism of congestive heart failure which are based upon analysis of interstitial fluid must be regarded with skepticism.

OBSERVATIONS INCOMPATIBLE WITH THE CLASSICAL CONCEPTS

There are certain observations which are difficult to accept in terms of the classical concepts of the mechanisms of congestive heart failure. Only a few will be mentioned, since it is not possible to include all of them in a presentation such as this. Most of these are incompatible with the backward failure concept, once most generally accepted to explain the syndrome observed in congestive heart failure.

(1) Although an increase in venous pressure probably contributes to the clinical picture, it is not feasible to attribute the edema and syndrome of congestive heart failure to this alone, for clinical states with *venous hypertension* are known to exist with little or no clinical evidence of edema. For example, following ligation of the inferior vena cava for therapeutic reasons, pressure in the veins of the feet, with these parts at the level of the heart, has been observed to exceed 600 mm. of water in the absence of any appreciable clinical evidence of edema (13 14) Edema of the

feet is not more apt to develop in the feet of a tall man than in those of a short man when standing. Patients with cardiac tamponade from concretio cordis may have generalized venous hypertension for many months without edema or the syndrome of congestive heart failure. Yet with prolonged continuation of the tamponade something does occur in such a patient to produce the typical clinical syndrome. Factors such as infection and exertion (15) are likely to precipitate the syndrome. Apparently some sequence of physiologic events must supervene before the picture of heart failure develops.

(2) Although the *pressure in the capillaries* of the feet of a tall man standing exceeds the pressure in the arteries of his arms, edema of the feet does not ordinarily develop It is unlikely therefore, that the slight rise in capillary hydrostatic pressure accompanying congestive heart failure could be completely responsible for the edema and the syndrome when even extreme elevations in capillary pressure of the feet are not associated with detectable edema there.

(3) Many severe chronic *anoxic states* are known to exist in the absence of edema or the clinical syndrome of congestive heart failure For example, high altitudes congenital cardiac defects with right to-left shunts, and chronic pulmonary disease are among the well known clinical factors accompanied by generalized anoxia of the tissues in which the syndrome of congestive failure does not develop because of the oxygen deficiency alone. It is, therefore, unlikely that asphyxia or anoxia of the cells of the body generally or of any in particular is solely responsible for this syndrome Patients sometimes have severe cyanosis in association with congenital cardiac disease such as the tetralogy of Fallot and yet live for many months or years before the pattern of heart failure develops. Just what

mechanism is set into motion, how and where it is initiated, and details of the chain of physiologic events which follow the initiating trigger mechanism remain unknown.

(4) A decrease in *cardiac output* has been agreed upon by most observers as the one necessary and truly primary physiologic phenomenon concerned with production of this clinical syndrome. Measurements of cardiac output obtained by various investigators in the presence of the syndrome have differed considerably varying from normal to reduced to elevated values (16 17 18 19, 20) Although the investigations have been accepted as satisfactory there have been obvious causes for differences in results. First, the methods employed for measurement of cardiac output are subject to error The exact degree of accuracy has never been adequately determined for an intact man in congestive heart failure. A great number of experiments would be required for a statistical evaluation, and even then it is doubtful that the answer would be obtained. Furthermore, because investigators have employed different methods for *measuring cardiac output, attempts to compare these data* have been rather unsatisfactory

Differences in interpretations of data among investigators have also arisen from failure to define or even to recognize precisely the phase or state of the failure during the measurement of cardiac output Two patients who are waterlogged and have clinical evidence of severe congestive heart failure may appear to be in the same state of failure yet in one the disease may be progressively worsening whereas in the other it may be stationary or improving Only with careful clinical study may relatively gross differences among patients be discovered and in fact, our present facilities may not even permit detection of significant differences. Furthermore it is not known what constitutes a significant difference. In many instances the patients studied have re

ceived therapy of varying types such as morphine oxygen, bed rest, sedatives, or other agents which are known to influence the clinical syndrome. For an investigator to state that his patient had received no therapy because digitalis or a mercurial diuretic had not been administered is only to oversimplify a complex problem.

Whereas an increase in cardiac output would be expected to be associated with or to precede improvement, this has not actually been observed in all instances (16 20) Venesection has been reported to decrease cardiac output and still result in improvement of the patient (16) The mechanism and significance of these observations have not been completely evaluated regardless of the point of view entertained.

To explain the discrepancies in patients in failure with high cardiac output there have been introduced the concepts of "high" and "low" output failure. Certain clinical states, such as severe anemia and thyrotoxicosis, are known to be associated with higher cardiac output than certain other cardiac diseases studied under apparently identical circumstances. It is, therefore suggested that the resting output may be higher in patients with thyrotoxic or anemic heart disease and congestive heart failure than in a patient with arteriosclerotic heart disease and an apparently comparable state of failure though both groups of patients are considered to have an insufficient output for the requirements of the tissues. This seems logical and may account for differences reported among investigators studying the problem, but some caution in accepting this concept completely is warranted in view of the complexity of the problem of chronic congestive heart failure. For the present therefore cautious acceptance of high and low output failure concepts may be advisable because of its usefulness in thought.

Another aspect of cardiac output which has offered difficulty is concerned with its relationship to venous pressure. Investigators continue to test the validity of Starling's law of the heart by employing measurements of pressure obtained in the right atrium or large veins as an index of ventricular filling. This is, of course, inaccurate, since the venous pressure or intra atrial pressure is not necessarily an index of the degree of ventricular filling or presystolic lengthening of the ventricular muscle fibers. Testing the correlation of the magnitude of cardiac output with these pressures can serve little useful purpose as an evaluation of Starling's law and its relationship to the concept of backward failure. It is not surprising, therefore, that many observers have been able to find no relationship between cardiac output and these pressures or the clinical syndrome of congestive heart failure. This is probably related in large measure to lack of relationship between maximal diastolic ventricular volume and venous pressure, the type and circumstances of the methods of study state of the failure, pre-existing therapy and other variables difficult or impossible to evaluate. Furthermore, cardiac output and venous pressure would not even be expected to be invariably correlated anyway

Cardiac output and function observed with the subject at rest in bed is not necessarily an index of the situation during exertion (21) To use the former as a basis for speculation on the latter may lead to serious error Observations during exertion in subjects with developing or progressive failure are particularly lacking. Furthermore, the forcing of fluids and electrolytes in patients in bed with impaired cardiac function in order to "produce" failure may also introduce error This may be a satisfactory procedure for studying certain aspects of water and electrolyte equilibrium or renal function during a positive balance of water and elec

trolytes but it does not necessarily represent progressive failure insofar as the heart as a pump is concerned. The rate of intake of water and electrolytes will mainly influence the rate with which the clinical syndrome especially the edema, will develop

The foregoing comments are presented to illustrate further the complexity of the problem. It is evident that data concerning cardiac output must be studied carefully before being accepted or related to congestive failure. It will also become obvious that the crucial changes in cardiac out put which initiate the clinical syndrome of congestive heart failure may exist for only a few beats of the heart or for too short a time to permit their observation by methods presently available.

(5) Since the *protein content* of cardiac edema fluid is not considered to be greater than that of normal interstitial fluid, an increase in capillary permeability is not likely to be significantly concerned with the edema of congestive heart failure. However the entire subject of capillary perme ability is little understood. Furthermore capillaries are freely permeable to water and electrolytes. Diffusion studies with radiosodium and radiochlorine in normal man and in patients with chronic congestive heart failure have failed to show differences which could be attributed to variations in capillary permeability (22 23 24) Variations in perme ability were not definitely excluded by these studies, but it is extremely unlikely that capillary permeability is impli cated in the development of the edema of congestive heart failure. Other mechanisms must be responsible for the syn drome (18)

(6) It has not been possible to produce the clinical syn drome of congestive heart failure in experimental animals even when practically all of the right *ventricular muscula ture* has been destroyed (25 26) Certainly however it

seems reasonable to suppose that this ventricle must fail to pump blood onward as efficiently as normally According to the backward failure concept, blood should dam behind this ventricle. This does not happen, however even following extensive or almost complete destruction of the musculature of the right ventricle. Therefore, either the concept of backward failure is erroneous or right ventricular musculature is not necessary to overcome resistance to blood flow in the pulmonary circuit. It is more likely that the former concept as presented is incorrect. However it must be remembered that even if all the right ventricular musculature is destroyed, the pressure within the right ventricular cavity may be raised by the contracting contiguous left ventricle (25)

(7) Certain procedures, such as low-salt diet or administration of mercurial diuretics, are known to have beneficial influences upon the clinical syndrome, including disappearance of edema, decline in venous pressure, and reduction in size of the liver without having any known *direct effect upon the heart* (3 27) It is inconceivable how a low sodium diet acts favorably on chronic congestive heart failure in terms of the "dam in the stream" concept of backward failure. Mercurial diuretics act primarily upon the kidneys without having any known significant effect upon the heart yet the clinical syndrome improves with their administration. It is difficult to comprehend how diuretics would be helpful if chronic congestive heart failure were merely a disturbance in hemodynamics, as presented by the backward failure or the forward failure concept.

(8) A syndrome with manifestations similar to those of chronic congestive heart failure can be produced by excessive administration of *desoxycorticosterone acetate* (DCA) which is not considered to have any significant direct cardiac

action. This point in the argument must be considered cautiously because large doses of DCA have been shown to produce histologic changes in the myocardium. Furthermore, administration of large quantities of sodium and water will tend to produce or aggravate the syndrome in a patient with "poor cardiac reserve." These procedures act upon extracardiac mechanisms and apparently contribute to the clinical pattern referred to as the sequelae of failure of the heart as a pump

Administration of large amounts of water and electrolytes to patients with anuria or oliguria due to renal disease will produce a similar syndrome. This, however by *definition* is not congestive heart failure.

It is evident from the foregoing discussions that the clinical pattern of chronic congestive heart failure or passive congestion cannot develop from merely a "dam in the stream." To consider this statement more carefully it is essential that the hemodynamic principles presented to explain the concepts of backward and forward failure be reexamined in some detail to uncover possible errors.

TWO CONCEPTS OF DEFINITION

Prior to a discussion of hemodynamic principles, it should be pointed out that:

(1) When congestive heart failure is designated as the syndrome under consideration, it is, by virtue of nomenclature necessary that the heart be involved in its mechanism. The identical clinical syndrome may be encountered in other disease states but these symptoms and signs are not *pathognomonic* of heart failure. It is likely that the syndrome of anasarca, venous hypertension, hepatomegaly and so forth may have several primary underlying causes just as fever and its associated manifestations may be produced by many fac

tors other than infection. When the syndrome appears in a previously normal animal following administration of DCA, the abnormal physiologic state is DCA intoxication and not heart failure. Only when the clinical syndrome is produced primarily as a result of disease of the heart should it be considered as congestive heart failure. *Therefore congestive heart failure is by definition, due to cardiac disease* Thus, the syndrome cannot be classified as heart failure if the cardiac state is normal in all respects.

It is generally assumed that the syndrome occurs only when the heart fails mechanically as a pump and whereas this concept is probably correct, it has not yet been unequivocally established. It has not been proved that the syndrome cannot develop as a result of cardiac disease without mechanical failure of the heart as a pump A theory to support this idea may easily be advanced with but a single plausible assumption. In order to permit continuation of this discussion, however it will be accepted that in congestive heart failure the heart first fails as a pump

(2) The clinical syndrome of edema, ascites, pleural effusion, basal pulmonary râles, hepatomegaly dyspnea, and so forth occurs as a result of cardiac dysfunction, probably failure of the pump to eject a sufficient volume of blood. As stated previously these sequelae, rather than the heart itself have been under observation by most investigators studying congestive heart failure. Obviously there is much to learn about these sequelae, particularly changes in the physiologic state responsible for and associated with them.

HEMODYNAMIC CONSIDERATIONS OF CONGESTIVE HEART FAILURE

With the assumption that the clinical syndrome of congestive heart failure is produced by failure of the heart as a

CIRCULATORY CIRCUIT ONE PUMP SYSTEM

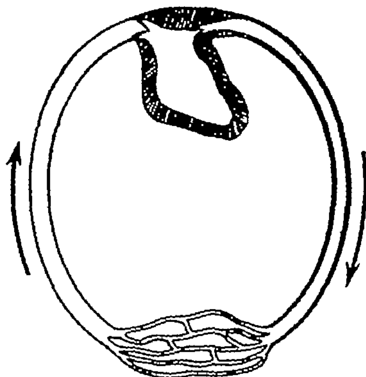


Figure 3. Diagram of circulatory circuit with single pump. In this and the other diagrams of the circulatory circuit, it is assumed that the subject is resting horizontally. Consult text for details.

pump we shall next consider the hemodynamic consequences of failure of the pump

The Circulatory Circuit with One Pump

Consider a pump circulating water around a circular ditch. As long as the pump continues to operate, the water will flow around in the ditch. The energy generated by the pump is lost overcoming the friction due to the flowing water Should the pump fail the water would simply stop flowing It would not dam behind the pump and produce a "congestion" in the portion of the ditch returning water to the pump *The same should be true if the ditch were a closed* vascular system with one ventricle generating the energy necessary to force blood around the circuit (Fig. 3) Therefore, failure of a single pump in a vascular circuit should not be expected to produce congestion in the circuit.

The Circulatory Circuit with Two Pumps

The human vascular system is supplied by two pumps, the right and left ventricles of the heart. This situation poses a different hemodynamic condition from that involving a circulatory circuit supplied by a single pump described in the preceding paragraph. Before various aspects of the hemodynamic consequences of failure of one or the other pump in the two-pump circulatory circuit are discussed, certain physiologic conditions must be noted.

The *total blood volume* of an average sized man is about 5,000 cc., about 500 cc. of which is in the pulmonary circulatory circuit and about 4,500 cc. in the systemic circuit. It is important to remember that the potential capacity of the systemic venous system is large and, therefore, the relative volumes of blood *in the systemic and pulmonary venous sys-*

CIRCULATORY CIRCUIT ONE PUMP SYSTEM

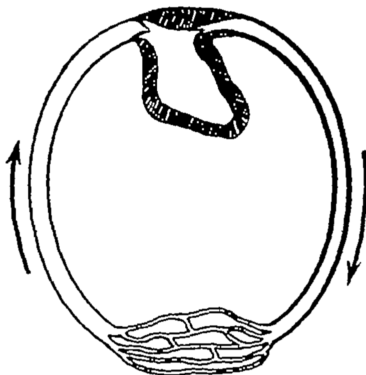


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STATIC CIRCULATORY PRESSURE

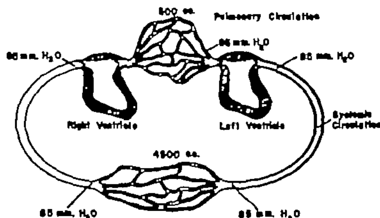


Figure 5 The circulatory circuit is shown with the circulation at rested. The system f tubes is patent and continuous. The heart hav ing stopped beating, static systemic vascular pressure of pproxi mately 85 mm. of water is reached throughout. When the heart stops beating, the distribution of blood is different from that when the circulation is ctive. Blood is shifted from the arterial side f the circulation, where the pressure is high and the vascular record strong, to the venous portion, where the pressure is lower and the vessels more distensible.

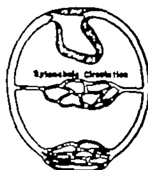
again developed. The differences in pressure began to develop at the first beat. Starr (4) obtained similar data in man at death and in his constructed model of the vascular system. Curiously enough, Starling found the pressure in the portal vein of the dog to remain essentially the same whether or not the blood was flowing

The skeletal and smooth muscles, gravity and elastic tissues of the body are among other factors which con tribute energy to the blood within the vascular system. Except for gravity these factors make their greatest con tribution to the pliable venous portion of the vascular sys- tem (28)

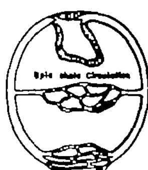
THE VASCULAR SYSTEM, BLOOD VOLUME AND BLOOD PRESSURE

The blood in the vascular system is incompressible. The walls of the vessels enclose or "fit around" the blood, the pressure of the blood within the vessels being determined by the "tightness" with which the vessels fit around the blood. Thus, the blood pressure in the vascular system is determined by the "tone" of the vessels or the volume of the blood or both. Obviously there can be no disproportion between the volume of the vascular bed and the blood volume. They are always equal in a closed vascular system, even in the presence of surgical and medical shock. When the blood pressure is higher in a given segment of the vascular system, the vessels *fit more tightly around or squeeze"* more tightly upon the blood within. Conversely when the walls squeeze less tightly the pressure declines. During such periods of variations in "tightness of fit" the volume of the blood or vascular bed does not change, since the blood is incompressible and unexpandable (Fig 6) If the volume of blood should increase, the volume of the vascular system must expand equally If the vascular walls are stretched or pressed upon from within by an increase in blood volume, the blood pressure within must increase, since the walls are resisting distention. If the tone of the entire vascular system should increase proportionately throughout without a change in blood volume, then the blood pressure throughout would also increase proportionately The reverse would be true if the vascular tone should decrease. With either state of vascular tone, the blood volume and the volume of the vascular bed would invariably be equal. If there were no change in blood volume under either condition, there would be no vasoconstriction or vasodilatation, i.e., the vessels

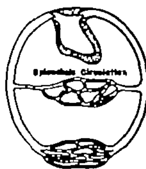
CHANGE IN GENERAL VASCULAR TONE AND IN BLOOD VOLUME



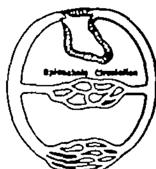
A. Blood Volume and Tone Normal



B. Generalized Vasoconstriction



C. Generalized Vasodilatation



D. Increased Total Blood Volume

Figure 6. Relationship of vascular tone to blood volume. The volume of the vascular bed and blood contained within are always equal. (A) Normal vascular tone throughout the circulatory system. (B) Generalized "vasoconstriction" or more accurately generalized increase in vascular tone or tightness of squeeze of the vascular system on the blood within. This increase in tone does not generally result in change in volume of the vascular system or blood within or in change in distribution of blood. It merely results in generalized rise in intravascular pressure. (C) Generalized vasodilatation or preferably termed generalized decrease in vascular tone or decreased squeeze of the vascular system on the blood within. Since blood is incompressible and unexpandable the volume of the vascular

(continued page 25)

would not decrease or increase in volume. They would merely tighten or loosen their "squeeze" on the blood within. It is for this reason that the terms "generalized vasoconstriction" and "generalized vasodilatation" may be misnomers or at least, may lead to errors in thought.

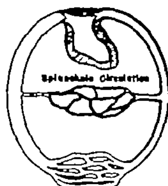
It is obvious, however that there may actually be localized constriction or dilatation within the vascular system (Fig. 7) i.e., there may be a local reduction or enlargement in the volume of the vascular system. When this occurs, the total blood volume and total volume of the vascular bed need not and probably do not change, and, of course, both always remain equal. For example, if the vessels of the splanchnic area undergo vasoconstriction and decrease in volume by 200 cc., then exactly 200 cc. of blood is squeezed out of these vessels. The blood is shifted into other portions of the vascular system, which must dilate or increase in volume by exactly this same amount to accommodate the shifted blood (Fig. 7) Conversely if the vessels of the splanchnic area dilate, so that the volume increases by 200 cc., then exactly 200 cc. more blood must flow into these vessels. This additional amount must be transferred from other portions of the vascular system, which must therefore decrease in volume by 200 cc. (Fig. 7) The concept of ***hemometakinesia*** was introduced to define this constant shifting or lending and borrowing of blood among different portions of the vascular system (29 30)

Thus whenever the pressure increases in any given seg

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system and blood within remain unchanged, but since the squeezing force on the blood is diminished, there is generalized decline in intravascular pressure. (D) Increase in blood volume, causing an equal increase in vascular volume. The change in pressure associated with this is determined by the tightness with which the vessels squeeze on the blood within. Should they distend readily the pressure would rise only slightly but should they resist distention, the pressure would rise to higher level.

LOCAL VARIATIONS IN VASCULAR TONE



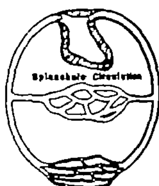


Figure 7 Local variations in vascular tone may affect the volume of the vascular bed and blood locally For example, with splanchnic vasoconstriction, blood is squeezed out of the splanchnic area into other vessels, which must expand an equal volume to accommodate the displaced blood. With splanchnic vasodilatation, blood volume and volume of the splanchnic vessel increase equally but blood must be shifted to them from other vessels, which narrow by an equal volume. During local vasoconstriction or vasodilatation, the volume of blood remains equal to the vascular system generally as well as locally and the total volume of blood and vascular system need not change.

ment of the vascular system, for example, the veins, either one or both of the following phenomena must have occurred (1) the vascular tone or tightness with which the walls of the vessels squeeze upon the blood within must have increased or (2) the volume of blood within must have increased and thus stretched the walls of the vessels (Fig. 8) This should be remembered whenever a change in venous pressure in congestive heart failure is under consideration.

Starling showed many years ago that when the circulation ceases for 20 to 40 seconds, the resulting cerebral ischemia causes the mean systemic pressure to rise two- to threefold. This "generalized" vasoconstriction includes the venous sys-

RELATION OF VENOUS TONE AND BLOOD VOLUME TO VENOUS PRESSURE

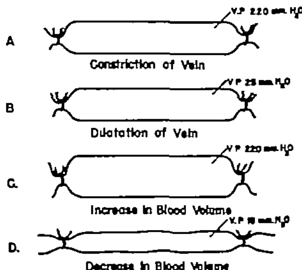


Figure 8. Segments of veins showing relationship of venous *tone* and blood volume to venous pressure. A and B show no change in volume of the segment but considerable change in the pressure within. In A there is venoconstriction or tightening of the vascular wall on the blood within, causing an increase in venous tone. B shows "venodilatation," with less squeezing on the contained blood and consequent decrease in venous tone. It is obvious that the terms constriction and dilatation are misleading in that there is no decrease or increase in the volume of the venous segment since blood is incompressible and unexpandable. The term "*tone*" is probably a better one to employ when there is no change in volume. C and D show changes in venous pressure within the venous segment produced by an increase or decrease in blood volume within the segment and secondarily by the stretch placed upon the venous wall.

circulation would not be expected as a result of the shift alone. This should produce no greater disturbance in the systemic circulation than a transfusion of 500 cc. of blood. In both instances because of the low pressure and great distensibility of the venous system, the blood would find its way into the veins or venous reservoir The veins would distend and if their "tone or "tightness of squeeze" remained constant the venous volume would increase without an associated significant rise in venous pressure. Such a response of veins to a relatively small increase in blood within them is normal (33) After some time, blood would reaccumulate in the pulmonary vessels and a new steady state would be reached with both ventricles ejecting 59 cc. per beat. Actually there are slight differences in output between the two ventricles from moment to moment, with the mean output being equal over a period of a few beats.

If the discrepancy between stroke volume of the right and left ventricles were greater and the cardiac rate were still 100, then the pulmonary vessels would become evacuated more rapidly For example, if the right ventricle failed and ejected 55 cc. per beat while the left ventricle ejected 60 cc., the pulmonary vessels would theoretically be expected to be emptied in one minute. Thus, the crucial changes may take place too rapidly to be readily observed.

It is evident, therefore, that merely failure of the right ventricle to pump sufficiently cannot cause an elevation in venous pressure because of damming of blood behind the right ventricle. Only a slight or no rise in venous pressure would be expected to occur if there were simply a dam in the stream. If on the other hand failure of the heart as a pump were the initiating cause for the clinical syndrome of congestive heart failure then other factors would have to participate

Incidentally it is apparent from the foregoing discussion

that if the venae cavae entering the right atrium were sud denly occluded by means of a hemostat (Fig. 10) there should be no more significant damming of blood behind the heart than Starling found when he made the dog's heart suddenly stop beating by vagal stimulation. If the venae cavae should become completely occluded the stroke output of the right ventricle would suddenly decline to zero. The left ventricle would drain the pulmonary vessels of blood within a few beats and then the output of the left ventricle would become zero The arterial blood pressure would fall, blood would be shifted to the systemic veins from the pul monary vessels and systemic arterial system, and the static systemic pressure would be obtained. The resilient and dis tensible veins would accommodate the blood shifted to them from the vessels of higher pressure with little change in

COMPLETE OBSTRUCTION OF FLOW INTO RIGHT VENTRICLE

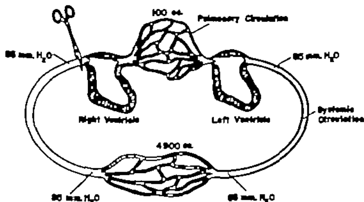


Figure 10. Complete obstruction of the return flow to the right ventricle, produced by clamp This causes the intravascular pressure to reach the static systemic level. Consult text for details.

venous pressure. A rise in venous pressure to high levels could only be brought about by an increase in the tightness with which the veins squeezed upon the blood within. *Without* this increase in venous tone, no significant rise in venous pressure would be expected. Exercise of skeletal muscle or pressure upon the liver will increase the pressure in the veins in direct proportion to the tightness or tone of the venous system. Merely a dam in the stream located in or near the right atrium would therefore not be expected to produce severe venous hypertension or congestion of blood under pressure.

On the other hand, in obstruction to the pulmonary veins or in pure mitral stenosis, the hemodynamic disturbances produced in the pulmonary vessels would differ considerably from those described with clamping of the superior and inferior venae cavae For example, with obstruction of the pulmonary veins blood pumped by the right ventricle would tend to accumulate behind the obstruction. Since the systemic blood volume is relatively large and the potential volume of the pulmonary vascular system relatively small, the additional blood forced into the latter will increase either the vascular tone or stretching of the vessels or both and thus cause the pressure in the pulmonary veins as well as arteries to rise. This would increase hydrostatic pressure in the pulmonary vessels and produce the well known clinical manifestations of pulmonary intravascular hypertension. Pulmonary edema would develop readily since intracapillary pressure is also elevated. The clinical picture of pulmonary edema or "congestive heart failure" would develop The acuteness and severity of this picture would depend upon the rapidity and degree of development of the obstruction.

The hemodynamic pattern for mitral stenosis is similar to that described for obstruction to the pulmonary veins. The details of pressure and volume flow are obvious and are pre-

dictable. Although no clinical syndrome produced by spasm of the pulmonary vein has been described should such a clinical counterpart occur from local venous spasm or as a result of external pressure, the associated hemodynamic phenomena would be predictable.

That the syndrome develops in cardiac disease in association with an excess of intake over output of electrolytes and water is well known. It is possible that when the output of the ventricles drops below a certain *critical level* the other mechanisms producing the syndrome of congestive heart failure are set into motion by yet unknown processes. These may be humoral (hormonal included) acting generally and specifically upon the kidney to cause a decrease in urinary output. They may also be partially hemodynamic in nature, influencing glomerular filtration and renal blood flow These factors are discussed later in greater detail.

When the critical level of failure of the pumping mechanism is reached, the venous pressure may rise because of an increase in blood volume, due to retention of electrolytes and water or because of an increase in venous tone (possibly due to cerebral asphyxia or release of neurogenic or chemical venopressor substances) Surely either increased blood volume or increased venous tone alone or in combination can account for the elevation of the venous pressure. However it is unlikely that the changes in blood volume alone encountered in congestive heart failure are of sufficient magnitude to account for the change in venous pressure.

The fundamental mechanisms by which the complete clinical syndrome finally develops remain a puzzle, and the detailed nature of the trigger mechanism and the chain of events leading to the syndrome has not yet been discovered. Only limited aspects of these are known. The initiating mechanism of congestive heart failure may be related to the relative amount of decline in cardiac output, to circulatory

demands of the tissues or to cardiac insufficiency The following concept is often advanced. Cardiac reserve cannot be measured quantitatively not even as quantitatively as renal function. It is roughly estimated by means of the functional classification employed clinically (34) It may be assumed that normal cardiac function is 100 per cent, i.e., it is adequate to meet the needs of the body under ordinary demands of human activity As with any other organ of the body cardiac function can probably be reduced to some degree without significantly interfering with circulation to the tissues. However with continued decline in function cardiac output becomes insufficient to supply certain demands placed upon it. With mild failure it may not be able to cope with the demands of strenuous exercise but may satisfy lesser needs With more extensive failure, the heart cannot even meet the demands placed upon it during ordinary living or even during bed rest. When the demands exceed the cardiac functional capacity for a sufficiently long period, the mechanisms concerned with producing the syndrome of congestive heart failure are activated and the resulting chain of events which lead to the clinical syndrome are set into motion.

Under most clinical circumstances congestive heart failure begins slowly presenting diurnal variations. During the day when the demands placed upon the heart are greatest, the demands of the tissues cannot be satisfied so that edema and other associated manifestations develop During the night, when the individual is in bed the demands of the tissues decline to a level below the *maximal functional capacity* of the heart, and compensation sets in. This day-and night cycle of relative failure and relative compensation may continue for weeks If each day for example the physiologic phenomena of failure exceed the amount of compensation achieved during the night, the sum total phenomena of fail

ure accumulated over a period of several days or weeks will be great enough to be manifested clinically The nature of the cycle and rate of change may vary considerably depending upon the activity diet, presence of infections, therapy severity of the cardiac disease and many other factors operative in the subject.

In the case of "high output" failure, even though the output is relatively high by comparison with the usual instances of heart failure, it is still insufficient to meet the current tissue needs, so that certain mechanisms are initiated and the syndrome of congestive failure develops. It must be remembered that these concepts are purely speculative being based primarily upon indirect evidence and reasoning

Failure of the Left Ventricle

When the left ventricle fails in the two-pump circulatory circuit, the hemodynamic outcome is different from that described for failure of the right ventricle. For example, when each of the two ventricles ejects 60 cc. per stroke, the circulation is maintained in a normal state. If the left ventricle fails slightly ejecting only 59 cc. per stroke, then 1 cc. more blood will be pumped by the right ventricle than by the left (Fig. 11) This results in an accumulation in the pulmonary vessels of 100 cc. blood per minute, if the cardiac rate is 100. In five minutes 500 cc. would be shifted from the systemic circulation into the pulmonary system. Because of the relatively large volume of the systemic circulation, a sufficient quantity of blood may be shifted into the pulmonary vessels to produce congestion and the clinical picture of acute pulmonary edema or "left ventricular congestive heart failure." Therefore, the syndrome of pure left ventricular failure is possible on the basis of congestion or a dam in the stream alone. The greater the discrepancies between the outputs of

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FAILURE OF BOTH VENTRICLES SIMULTANEOUSLY

If it is assumed that the syndrome of congestive heart failure is produced by equal and simultaneous failure of both ventricles, the changes in the hemodynamic state would be similar to those described for failure of the single pump of the circulatory circuit in a one-pump system. There obviously could be no damming of blood in the stream, for reasons discussed previously No more fluid would accumulate behind any one ventricle than if two pumps situated fairly closely together in a circular ditch simultaneously failed equally to some degree but continued to pump equal volumes of water around the ditch. The water would remain equally distributed throughout the ditch and no damming of water would occur

Should both ventricles fail simultaneously but unequally then the hemodynamic changes expected would depend upon which ventricle failed to the greater degree. The results of both of these situations have been described. It is evident that failure of both ventricles simultaneously does not significantly modify the hemodynamic principles previously described for failure of the "pump"

ROLE OF THE KIDNEYS

From the foregoing discussion, it is evident that, except for acute left ventricular failure, the entire clinical syndrome of chronic congestive heart failure cannot develop from disturbances in hemodynamics alone. Other physiologic processes are necessary for the development of the syndrome.

There are certain physiologic processes which function during the development of the syndrome:

(1) The syndrome by definition begins with disturbances in the heart.

(2) The water and electrolytes which are retained enter through the gastrointestinal tract, and there is no evidence that the intake is abnormally large

(3) Renal excretion of water and electrolytes must be less than intake, for a positive balance is a prerequisite to the development of anasarca. Since the intake is essentially constant, renal function must change in such a way that urinary output diminishes.

Clinicians have known for many years that a renal factor exists in congestive heart failure. Patients with progressive congestive heart failure are known to have scanty highly colored urine of high specific gravity containing albumin, casts and erythrocytes. Intake of electrolytes and water is known to produce exacerbations of the syndrome That renal function is only temporarily disturbed or altered is evidenced by the rapid return of previous renal function with the onset of compensation and diuresis. Furthermore, administration of a mercurial diuretic to a patient in congestive heart failure with reduced urinary output, including sodium and water promptly produces diuresis Such a response is not obtained in a patient with terminal nephritis. Thus, it is evident that the kidneys are not diseased in uncomplicated congestive heart failure and whereas they may function differently this is not necessarily abnormal for such a cardiac state. Furthermore an intake of sodium below the level of output results in clinical improvement.

Renal Function

Studies of renal function (35 36 37 38 39 40, 41 42) have shown that it is altered during cardiac decompensation. As with cardiac output, results have varied with the degree

and stage of the failure. Not only is the state of the failure important but so are its duration, acuteness of onset and chronicity (40) as well as the general psychic and physical state of the subject under study and errors in clearance methods (36 37 38 39 41 42) These variations in results have naturally led to differences in conclusions and to some confusion concerning the renal physiology associated with failure. Therefore, with the data available it is not possible to define precisely the renal function or changes in renal function associated with this syndrome. The physiologic renal state presented here represents the one most generally accepted by those engaged in such studies. It is well to realize that deviations may be considerable.

In general, *effective renal plasma flow* (RPF) has been found to decline from a mean normal value of about 600 to as low as 200 cc./mm./1 73 m² (Fig. 12) *Glomerular filtra*

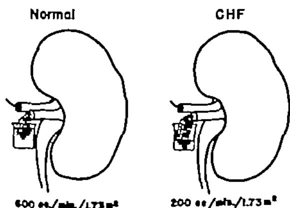


Figure 12. Effective renal plasma flow changed from an average normal of 600 cc. to 200 cc./min./1 73 m²

(1) The syndrome, by definition, begins with disturbances in the heart.

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FILTRATION FRACTION INCREASED IN CONGESTIVE HEART FAILURE

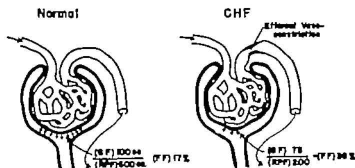


Figure 4. Filtration fraction may be increased more than twofold in congestive heart failure. This apparently occurs because of constriction of the efferent glomerular arterioles.

the glomeruli. The significance of the decline in maximal tubular capacity is not clear

There is no general agreement about how and why renal function changes in congestive heart failure. Many investigators are currently interested in this. Almost everyone agrees that there is more complete tubular reabsorption of sodium from the glomerular filtrate as it passes through the nephrons (Fig 15) Although the mechanism by which this occurs remains obscure, some observers (43 44) have interpreted their data to indicate that the increased tubular reabsorption is localized in the distal tubules. The experiments do not unequivocally establish this concept, the conclusion being based upon crucial assumptions which have not been definitely proved as valid. Furthermore, studies in this field have not demonstrated that changes in the hemodynamic state alone are sufficient to explain all the changes in renal function observed in congestive heart failure. Considerable data (3 45 46 47) indicate that humoral or chemical fac

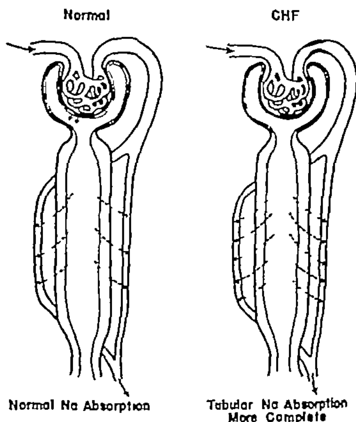


Figure 5. The tubules reabsorb sodium more completely in congestive heart failure. The mechanism and precise location of this reaction remain unknown.

tors mediated through the tubules are at least partially responsible for changes in renal function.

None of the renal studies indicate primary renal disease only altered function has been observed. Whether or not this change in function is compensatory or obligatory remains controversial at present, but it is probably both.

ROLE OF THE ENDOCRINE SYSTEM

Because of the relatively rapid rate with which the changes in renal function occur and because of the nature of these changes, it has been suggested by those interested in the problem that excretion of sodium and water decreases as a result of excessive production or failure of inactivation of water and electrolyte retaining hormones (3, 42, 45, 48, 49). To date evidence for this is indirect and speculative, based upon the close similarity of the urinary changes observed in congestive heart failure to those associated with administration of adrenocorticotrophic hormone (ACTH), desoxycorticosterone acetate (DCA), and other steroids. Obviously the suprarenal and pituitary glands have been considered the sites of the hormone production. These concepts may eventually prove to be true but today they remain speculative. That which appears to be most logical does not always finally prove to be the true mechanism.

It is possible to propose a chemical chain of events to explain the mechanism for electrolyte and water retention mediated through the kidneys in which the primarily responsible chemical agent acts as an inhibitor or an activator but the mechanism for the activation of such an agent is unknown. This chemical chain of events is probably extremely complex, as are most of the known metabolic processes. The pituitary and adrenal glands may be and probably are concerned with them, but this is not necessarily true.

Antidiuretic substances have been detected in the urine of patients with congestive heart failure (46) The presence of such a substance might be expected in the urine of any patient with non mechanical or functional oliguria, but its significance has not been established.

It may be concluded from speculation and evidence that a chemical mediator or chain of chemical processes is associated with retention of electrolytes and water as a possible cause of the reduced excretory function of the kidneys in congestive heart failure. Much more extensive research is yet required to clarify the problem, however It is not proposed to review here in detail the evidence for and against a chemical factor in congestive heart failure or to indicate the research requirements and discrepancies.

VENOUS HYPERTENSION

That generalized and symmetric venous hypertension is associated with congestive heart failure is generally accepted. The precise temporal relationship to each and all of the physiologic disturbances observed in the various stages of congestive heart failure have not yet been ascertained. Some observers contend that venous hypertension precedes the accumulation of fluid and electrolytes others believe it follows or coincides with the accumulation. The experimental data in support of either concept are insufficient to permit definite conclusions. Regardless of this however some theoretic considerations appear applicable.

For example it has been pointed out that venous hypertension cannot occur without either or both: (1) an increase in venous tone or "tightness of squeeze" of the venous walls upon the blood within; or (2) an increase in blood volume within the veins. If it is shown that venous pressure increases during the early stages of congestive heart failure, or when

the pump" or ventricle fails and before the patient accumulates water and salt, then either there is an increase in venous tone or the blood volume is increased at the expense of interstitial or intracellular water and electrolytes, or both of these occur If on the other hand, it is shown that the patient gains weight or accumulates water and salt before or simultaneously with a rise in venous pressure, then an increase in blood volume may be a factor but an increase in venous tone most likely also contributes to the venous hypertension, for the magnitude of increase in blood volume reported is not sufficient in itself to cause venous hypertension. Should there be no change in blood volume during the period of rise in venous pressure, then an increase in venous tone must be the direct cause of the venous hypertension, for it has been shown in the foregoing discussion that a shift of blood from the pulmonary circuit cannot cause an elevation in systemic venous pressure with failure of the pump alone.

Distended veins in the neck do not necessarily indicate an increase in blood volume. As stated previously (Fig 7) blood may be shifted from one portion of the circulation to another without a change in blood volume. The distended veins may therefore indicate a more intense localized venous tone or constriction of the more peripheral veins or at least, of veins elsewhere this is probably of nervous origin (50)

There are no satisfactory data to establish the presence or absence of an increase in venous tone during the developmental phases of the syndrome of congestive heart failure. The excellent studies of McMichael and his associates do not and, as designed, could not settle this point directly The state of venous tone is obviously an important problem which has received little, if any direct examination.

It is known that pressure over the liver (hepatojugular

reflux) or exercise results in an increase in venous pressure in patients with congestive heart failure, whereas it produces little or no rise in normal subjects. The mechanism for the elevation in venous pressure has likewise never been elucidated. If either the blood volume or the venous tone is increased, a definite elevation in venous pressure would be expected following pressure over the liver which displaces blood out of the liver or splanchnic vessels, or muscular activity with associated displacement of blood out of the veins within the skeletal muscles into the large systemic veins. With an already "tight" venous system, a slight placement of blood into it or merely pressure upon it will result in an increase in pressure within the system. In fact, it is probably more accurate to visualize pressure upon a "tight" venous system as the cause and not necessarily displacement of blood into it, for the system is really a single continuous system. In the normal subject, displacement of the blood into normal veins with normal tonal function and a normal content of blood would not be expected to produce a significant elevation in venous pressure. Under normal conditions normal veins accommodate a relatively large volume of blood without an increase in intravenous pressure (33) Furthermore, pressure upon a venous system of normal "tightness" with normal tonal function should understandably result in little or no increase in pressure within the system, especially when it is realized that normal veins will relax or decrease their tone or tightness to prevent venous hypertension. When the compensatory relaxation or loosening is excessive venous pressure may actually decline. This has been observed in normal man on many occasions. It is also possible that the venous tonal regulating mechanisms may be more sensitive to shifts in blood pressure upon the venous system, or to changes in venous hemodynamics in the subject with congestive failure than in the normal person,

resulting in an "over tightening" of their walls upon the blood within.

Experimental injury to the right ventricle to produce failure" of that ventricle results in a physiologic state in which exercise of skeletal muscles causes a rise in venous pressure (21) Such experiments are difficult to interpret because of the numerous variables involved and the complexity of the state of the experimental animal, including changes in blood pressure cardiac rate and possibly vascular tonal function. Before it can be concluded that venous hypertension is the result of a dam in the stream, the state of venous tone or reactivity of venous tone to a shift of blood into the systemic venous system must be evaluated. If venous tone were increased directly by contraction of the smooth muscles within the walls of the veins or increased by a *shift of blood* into the large systemic veins associated with a greater response to passive distention, then venous pressure would rise in association with exercise. Surely the level of venous pressure or a change in that level is not a reliable index of the accumulation or "damming" of blood behind a failing ventricle. That the level of venous pressure tends to bear a relationship to the clinical state of congestive heart failure is well known. A spontaneous rise o fall in venous pressure does not, by deduction, *a priori* however indicate the existence of or a change in a "dam in the circulatory stream" or suggest that congestive heart failure consists merely of passive congestion of blood in veins.

CLINICAL SUGGESTIONS

Whereas concepts concerning the mechanism of congestive heart failure have undergone revision during the past few years, no modification of the clinical management has been warranted. The use of morphine, oxygen, digitalis, low

reflux) or exercise results in an increase in venous pressure in patients with congestive heart failure, whereas it produces little or no rise in normal subjects. The mechanism for the elevation in venous pressure has likewise never been elucidated. If either the blood volume or the venous tone is increased a definite elevation in venous pressure would be expected following pressure over the liver which displaces blood out of the liver or splanchnic vessels, or muscular activity with associated displacement of blood out of the veins within the skeletal muscles into the large systemic veins. With an already "tight" venous system, a slight placement of blood into it or merely pressure upon it will result in an increase in pressure within the system. In fact it is probably more accurate to visualize pressure upon a "tight venous system as the cause and not necessarily displacement of blood into it, for the system is really a single continuous system. In the normal subject, displacement of the blood into normal veins with normal tonal function and a normal content of blood would not be expected to produce a significant elevation in venous pressure. Under normal conditions normal veins accommodate a relatively large volume of blood without an increase in intravenous pressure (33) Furthermore, pressure upon a venous system of normal "tightness" with normal tonal function should understandably result in little or no increase in pressure within the system, especially when it is realized that normal veins will relax or decrease their tone or tightness to prevent venous hypertension When the compensatory relaxation or loosening is excessive, venous pressure may actually decline. This has been observed in normal man on many occasions. It is also possible that the venous tonal regulating mechanisms may be more sensitive to shifts in blood pressure upon the venous system, or to changes in venous hemodynamics in the subject with congestive failure than in the normal person,

patients continues to be most successful by certain approaches.

A comparison may be made with diabetes mellitus. Its clinical management remains unchanged regardless of whether or not the concept of beta-oxidation of the fatty acids is correct. All therapy is not being discontinued until that point achieves complete clarification. Similarly the clinical management of congestive failure must remain empiric to some degree Terms with erroneous implications may continue to be employed for traditional reasons. This is permissible provided the clinician is thoroughly aware of the lack of knowledge concerning the mechanism of failure He should be prepared to alter his concepts whenever new data become adequately established. To change the terminology prematurely and without sufficient supporting evidence, however can only lead to further confusion.

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(CHAPTER TWO)

The Treatment of Congestive Heart Failure

BECAUSE congestive heart failure is so common and so poorly understood, this syndrome is one of the most important therapeutic problems confronting the clinician today. As previously discussed (1) even though the mechanism of right and left congestive heart failure continues to challenge investigators and although it is not even known whether congestive heart failure may, from the mechanistic point of view, justifiably be divided into the right and left types, clinicians have learned from many years of experience that when they encounter the syndromes (2, 3, 4) of right or left congestive failure, certain prognostic or therapeutic principles apply. Just as we do not discard the use of insulin in the treatment of diabetes because the details of its action remain unsolved, neither do we discontinue the treatment of patients with congestive heart failure simply because it persists as a complex and ill understood syndrome. Certain therapeutic procedures appear to benefit the patient with congestive failure, and if these are employed judiciously his condition will usually not become aggravated and will frequently even improve.

For purposes of simplicity, the treatment of *moderately*

severe uncomplicated chronic congestive heart failure will be reviewed. These procedures may be appropriately modified for patients with mild failure who are able to tolerate less haste in treatment as well as for those with severe or acute congestive failure who must be handled as a medical emergency requiring immediate, vigorous therapy Necessary modifications to meet the demands of the individual patient become evident from the following presentation. Complications such as infections, myocardial infarction, thromboembolism, pregnancy operations, and the like obviously also require therapeutic attention and will alter the therapeutic approach.

PROPHYLAXIS

Clearly the primary aim of the patient and the doctor should be the prevention of cardiac disease and therefore of congestive heart failure. Too little attention has been devoted to this phase of the problem. Clinical states known to produce cardiac disease, such as anemia, syphilis, infections and malnutrition, should be treated promptly and vigorously in order to prevent or minimize cardiac damage or at least, these etiologic factors should be removed before irreversible damage to the heart has occurred. Furthermore, *when more than one etiologic factor is active in the patient,* as many as possible should of course, be eliminated. If a patient with aortic valvular insufficiency is also anemic, his anemic state should be adequately treated, even though it is not yet possible to replace the insufficient aortic valve with a competent one. Elimination of the anemia often delays progress of the cardiac disease and, in turn, of failure.

Once a patient has developed irreversible cardiac disease, however attention should be directed toward prevention of the development of congestive heart failure The approach

to this problem varies with the age of the patient, extent of failure, presence or absence of debilitating or complicating states, his economic state and other factors. The general or basic principles and procedures will be presented in the following discussion.

MENTAL AND PHYSICAL WORK

The severity of the cardiac state should determine the amount of mental and physical work which a patient with irreversible cardiac disease may be permitted to do If the patient has cardiac disease of functional Class I (5) the extent of his activities would be governed by the etiologic factor concerned If the causative agent is rheumatic fever or syphilis which is no longer active, then this patient with chronic myocardial damage may lead the ordinary type of life with restriction in competitive sports and strenuous exercise, in order to avoid overtaxing his cardiac function. On the other hand, if in this same patient in whom the etiologic factor were no longer active, there were also serious valvular disease, with either mitral stenosis or aortic insufficiency physical and mental activity might be restricted further

Should the patient have arteriosclerotic heart disease or hypertension with heart disease, then it may be important to restrict his activity even more despite the fact that functional capacity may be of Class I. Under such circumstances, it is not possible to remove the etiologic factor and for this reason cardiac damage will progressively increase. It is therefore extremely important not to aggravate the etiologic factor; a sharp elevation in blood pressure for example, might impose an additional load upon the heart Such a patient might be advised to lead a sedentary life. If there is no progress in his diseased state, greater activity may be allowed

with continued observation. Modifications in activity may be made as the cardiac state warrants. Undue disturbances produced by emotional stress, worry and mental and physical fatigue from an active business, should be taken into consideration, and the patient should be properly advised regarding them. He should learn how to relax and avoid mental fatigue, should take frequent vacations and avoid long hours of work, and should use sedatives only if necessary for insomnia, restlessness and irritability He should be taught the general philosophic point of view which would encourage a more relaxed attitude rather than a tense one.

GENERAL HEALTH OF THE PATIENT

The general health of the patient should be carefully evaluated and, after complete inventory any disturbances in health should be properly managed. The patient should be advised regarding proper diet, problems of sleep rest, recreation, vacation and the usual hygienic measures. Fresh air regular hours, and all similar habits should be insisted upon. Maintenance of good health will remove from the heart any additional strain or damage which might follow a diseased state of a systemic or focal nature. Most people have never learned or have forgotten the general rules of good, healthy living, and these must be taught or reiterated to the patient when necessary

DRUGS

Drugs should be used only when necessary and in limited quantities. The patient who does not have congestive heart failure requires no drugs used for the treatment of failure. Drugs should be used only for prevention of this disease Medications such as digitalis should be employed not as pro-

phylactic agents but only for treatment of failure itself When the patient continues to have difficulties with restlessness, irritability and insomnia, despite proper diet, rest and recreation then sedatives may be employed sparingly but he should not become dependent upon them. They should be used only during periods of insomnia or restlessness and irritability at other times when the patient is feeling well, they should be avoided

THE MANAGEMENT OF CHRONIC, MODERATE AND SEVERE CONGESTIVE HEART FAILURE

Once congestive heart failure has developed, treatment directed towards its correction should begin immediately Immediate treatment, of course, necessitates early recognition of the state Unfortunately the patient himself thinking his symptoms will disappear often fails to see his doctor early enough, or the doctor fails to recognize early failure. In many instances, early failure escapes recognition because of too hasty an examination and unsatisfactory history Early failure is usually accompanied by symptoms particularly weakness and dyspnea. Edema may sometimes be present and can be detected on careful examination of the feet and legs. It is not the purpose of this discussion to enter into the management of early failure but approach to this problem will become obvious from the discussion to follow regarding therapeutic principles in early and mild, chronic, moderate and severe failure. Frequently either because of neglect on the part of the patient to see his physician or failure to recognize congestive heart failure early enough, a patient may enter into a stage of moderate or severe chronic failure before therapy for congestive heart failure is instituted. It is this type of patient that is under particular consideration in this presentation. If the failure is mild and

early much less vigorous therapy such as less rapid digitalization, is indicated.

Rest

The patient with moderate or severe congestive heart failure should be placed *in bed immediately*. *The welfare of the* patient and not the convenience of the physician should determine whether he is placed in bed in a hospital or at home. If a physician does not see patients at home, then he should truthfully inform his patient that he advises hospitalization not because it is necessary for the patient's welfare but for his own convenience. If the patient desires this particular physician's services, he will go to the hospital. If he wishes to remain at home, however, he may choose another physician who sees patients at home. Frequently and probably usually physicians insist upon hospitalizing patients because of the erroneous impression that only there can adequate therapy be obtained. This point has special significance in congestive heart failure. It seems ironic to impose hospital expenses of twenty dollars or more per day on a patient with limited funds and then advise him not to worry about finances. Congestive heart failure is one medical state which can be treated almost, if not equally, as well in the home as in the hospital, and therefore to insist that a patient must enter a hospital for the management of his failure is to misinterpret the facts. In most cities and with the methods of *transportation and services available today* one can obtain almost any of the necessary materials and apparatus for proper treatment of the patient in the home. Furthermore, most patients prefer being taken care of by members of their family and home treatment is usually a great deal more satisfactory in such instances.

Of all the procedures available in the management of con

gestive heart failure, rest is probably the most important. This includes mental as well as physical rest The patient should be placed preferably in a bed which will permit adequate comfort and nursing care. A comfortable clean, quiet, cheerful room is extremely important in the management of a patient who is to be bedridden for some time it will promote mental as well as physical relaxation. Initially it may not be necessary to provide a radio but later as the patient *improves, this may be advisable.*

Of great value in hot and humid environments is an air conditioned room (temperature 72-78 F and relative humidity not above 60 per cent) Patients are able to relax a great deal more and are more comfortable in such an environment than in a hot and humid one. Because many individuals crowded into a room can raise the environmental temperature and humidity considerably only those who are absolutely necessary for the patient's care or for diversional reasons should be allowed to enter

The nurse or other attendants should be pleasant and should handle the patient gently and with solicitude. No visitors should be permitted, and only one or two members of the family who are particularly well adapted for the management of sick persons should be allowed in the room. No one with a gloomy or pessimistic outlook should ever be allowed to see the patient. The nurse should be readily available, for if the patient has difficulty reaching her he may become exasperated or excited. Even the less excitable patients can become extremely irritated with some of the inferior hospital service encountered today The prime purpose of the nurse is to take care of the patient's needs immediately and tenderly rather than to supervise an outlined treatment. The physician should emphasize the extreme importance of nursing attention and its role in the final and favorable outcome of the patient's illness.

It is important to eliminate as many mental difficulties and worries as possible. A patient should be told that his main objective at the moment is to get well and he therefore should forget about business difficulties and other worries. Business associates should not be allowed to enter the patient's room for the purpose of discussing problems. No telephone should be available to the patient nor should any telephone messages be transmitted to him during this period. A great deal of attention should be directed toward his mental state in order to induce mental relaxation. A patient who is less active mentally and physically usually fares better than one who is excitable or easily disturbed. In many instances the physician fails to pay sufficient attention to these small details, which may not appear to have any significance to him but which are extremely important to the patient.

MORPHINE

If the patient is apprehensive and appears to be struggling morphine, ¼ grain or 15 milligrams subcutaneously should be administered promptly—as soon as the diagnosis has been established and therapy has begun. Smaller doses are inadequate and only delay relief of apprehension and struggling, for which the drug is primarily employed. Administration of the morphine should be repeated in 3 or 4 hours if necessary but one dose is usually adequate. When the failure improves and these psychic manifestations disappear then phenobarbital in adequate doses, 1 grain (60 milligrams) orally may be used if needed and as frequently as the situation requires. It is especially useful for insomnia.

It is not advisable to keep the patient under the constant influence of hypnotics and sedatives, although this is rather common practice. As much control of restlessness and irritability can be obtained by reassuring the patient and en-

couraging him to remain awake during the day so that he may be sleepy by nightfall. Furthermore, Demerol® has not been shown to have any place in the treatment of this syndrome and should not be used unless the patient is sensitive to morphine but not to Demerol®. Morphine is an old and dependable drug with which the medical profession has had much experience. Its side effects, especially its tendency to produce constipation, must be considered and especially for that reason should it be used sparingly. It should not be given to the patient who is calm and nonapprehensive.

OXYGEN

Oxygen should be used routinely, even in the absence of any detectable cyanosis. There must be about 5 grams of reduced hemoglobin per 100 cc. of circulating blood for cyanosis to be detected clinically and, therefore, subclinical amounts of anoxia may exist which it would be advisable to eliminate if possible. There are several methods of administering oxygen, among the most important of which are the following:

(1) Oxygen chamber. This apparatus is the best for administering oxygen. It consists of a specially constructed air-conditioned room with its O_2 and CO_2 contents controlled at any desired level and automatically recorded. The O_2 concentration is usually maintained at 55 per cent; higher concentrations are toxic when administered for long periods of time and are not necessary. The chemical and climatic conditions of these rooms may be properly controlled and are therefore superior. Unfortunately, however, they are expensive to build and operate and are available in only a few hospitals.

(2) Oxygen tent. This is the second best apparatus for administering oxygen, provided the tent is in good operating

condition no important leaks exist and extreme care is taken to tuck the tent tightly into the bed clothing in order to obtain O_2 concentration of 55 per cent within the tent. Its advantages include its inexpensiveness in initial cost and the fact that it is not too costly to operate. There are no discomforts from appliances attached directly to the patient. All fear and apprehension can be eliminated by properly presenting the problem and indications for its use to the patient. Furthermore, the cool environment around the patient produced by the tent eliminates extra loads on the heart caused by difficulties in thermal elimination and regulation. This is especially important on hot and humid days or in tropical and subtropical areas Cardiac work is increased by a hot and humid environment, a factor which is usually overlooked in the management of patients with cardiac disease. It has been shown that congestive heart failure can be precipitated or aggravated by a hot and humid environment (6 7) whereas a cool environment is particularly comfortable to such patients and is conducive to their physical and psychic relaxation.

(3) Nasal catheter This method should be employed when the preceding two are not available. The catheter should be placed into the nostril properly kept clean and changed three to four times daily Discomfort from pressure should be avoided The oxygen should flow at a rate of 10 liters per minute and should be well humidified by adequate bubbling through water

(4) Oxygen mask. The oxygen mask is usually not comfortable, and most patients refuse to wear it for more than a few hours at a time. With special effort the mask can be made fairly comfortable and may be tolerated. It should be kept clean and should be applied snugly but not tightly to insure good O_2 concentration. The O_2 should be adequately humidified by bubbling through water

DIGITALIS

The best preparation of digitalis for general purposes is the whole leaf which should be administered whenever possible. There is too great a tendency to use intravenously administered preparations for "rapid digitalization" of the patient with congestive heart failure whether he needs it or not. Such a practice should be reserved for those patients who are acutely and severely ill or for those with some gastrointestinal disturbance, which might make intestinal absorption of the whole leaf uncertain. It is possible to digitalize a patient with the whole leaf within 24 to 36 hours anyway a much slower rate of digitalization being indicated of course, in patients with early and mild failure.

As a guide, and only as a guide based upon data for the average patient, it has been found that about 1 unit (1 5 grains or 0.1 gram) of whole leaf per eight pounds of body weight is required to digitalize a patient. It must be remembered that each patient requires a different amount of this drug to produce digitalization and that the dosage mentioned is only an approximate or "rule of thumb" quantity The amount actually administered should be whatever is required to produce digitalization.

The Eggleston method is a good method of administration. For example if the patient weighs 160 lbs., he would require approximately 20 units or 20 1 5 grain-tablets of whole leaf digitalis. One half the calculated dose, or 10 tablets, is given immediately About six to eight hours later the full pharmacologic effect of the previous dose will have reached its maximum. At this time the patient should be examined carefully to determine whether digitalization has been produced by these first 10 units. Although this is unlikely it is necessary to be sure before the second dose is ad

ministered. If the patient is not digitalized, half the remaining dose, 5 units or 5 .1 5 gram tablets, is given. About six to eight hours following administration of the second dose, the patient should be examined again. If he is not yet digitalized, he should receive 2 units, or 2 .1 5 gram tablets, of digitalis every six to eight hours until he is fully digitalized. Before each two-unit dose, he should be checked by the physician in order to make sure that he has not yet been digitalized. Under such a regimen the patient would not be overdigitalized by more than two units, which is probably not dangerous. Furthermore, such a procedure should insure adequate digitalization. Once digitalization has been effected, a maintenance dose varying from 1 to 2 tablets daily should be instituted. It is important to make certain that the maintenance dose is adequate and that the patient is not being slowly over- or underdigitalized. This occurs frequently when a certain dose for maintenance is employed routinely. Remember that the rate of destruction and excretion of digitalis varies considerably from patient to patient and even from time to time in the same patient.

If the patient is too ill to take digitalis by mouth or has nausea and vomiting and cannot retain oral medication, then intravenous digitalization should be employed. Digitoxin, 1.2 milligrams intravenously, may be administered slowly followed in about six to eight hours by 0.2 to 0.4 milligram in order to establish digitalization. Or Cedilanid, 1.4 to 1.6 milligrams, may be given intravenously to achieve the same effect, followed by 0.2 milligram if the initial dose fails to establish digitalization. Then, it is possible to switch to the whole leaf as the patient improves.

It is extremely important to recognize the manifestations of digitalization. When a patient attains satisfactory digitalization, his general clinical appearance will improve. He will exhibit less apprehension, will look a great deal better

generally will become interested in his surroundings and himself and particularly in his home, family and environmental problems in general. His pulse rate will fall; one should attempt to maintain it at about 72 to 75 per minute. Diuresis will begin, dyspnea will be reduced and evidences of congestive heart failure on physical examination, such as râles in the chest and cough, will begin to disappear If the patient has been slightly overdigitalized he will begin to manifest premature beats. There may be coupling and paroxysms of tachycardia or even early manifestations of heart block, as evidenced electrocardiographically by prolongation of the PR interval. It should be remembered that patients with organic heart disease may have premature contractions independent of digitalis therapy For this reason the cardiac mechanism should be studied carefully before digitalization is initiated, for if premature beats existed before administration of digitalis, it is important not to attribute them later to the drug As a rule premature beats present before administration of the drug will disappear with digitalization. On the other hand, premature contractions which were not previously present and which become frequent at the time one would expect the patient to be digitalized are probably due to digitalis The physician, however should not discontinue the drug early in its administration simply because an occasional premature contraction occurs, particularly if it is supraventricular in origin.

When other therapeutic measures are not in progress, such as administration of mercurial diuretics or other types of diuretics, it is not too difficult to evaluate manifestations of improvement which result from digitalis therapy However when other procedures are being employed simultaneously it is entirely possible that diuresis for example may not be the result of digitalization but rather of mercurial diuretics. In such instances physicians assuming diuresis to be a mani

festation of digitalization, frequently reduce the dosage prematurely For this reason patients are frequently made quately digitalized. Similarly nausea and vomiting may be either an early sign of digitalis intoxication or they may be associated with the dyspepsia so frequently observed in patients with congestive heart failure. It is important to make this distinction. When these symptoms occur at the time that one would expect the effects of digitalization to be maximal, then they are likely to be related to digitalis therapy Sometimes nausea and vomiting will disappear if another preparation of digitalis is substituted.

Among the more advanced manifestations of digitalis intoxication are auricular fibrillation, flutter 211 auriculo-ventricular block, or higher degrees of A V block, including complete heart block, the tachycardias and finally of course, ventricular fibrillation. It must be remembered that there is no antidote for digitalis, but the therapeutic dose and the lethal dose are fairly widely separated. The aim in digitalis therapy is to achieve a therapeutic level in the body and not to administer the drug in quantities that will produce serious intoxication. Most instances of underdigitalization are due to fear on the part of the physician, of overdigitalization. If excessive digitalis has been administered, the drug should, of course, be discontinued immediately and the patient should be carefully observed, administration being reinstituted when manifestations of intoxication have disappeared and those of full, adequate digitalization have appeared. The subject of digitalis will be presented in greater detail in Chapter Four

Diet

Most patients who go into congestive heart failure are not particularly concerned about eating, especially during the

first day of treatment. During this time probably the simplest diet and one which is certainly adequate is the Karell diet, consisting of 800 cc. of milk daily On the next day the patient may be placed on a soft, bland diet low in sodium, containing not more than about 1 7 grams sodium chloride daily The diet should consist of such foods as mashed potatoes toast, butter soft-boiled egg, milk, tea, coffee and the like. As the patient improves, the foods may be increased in number and variety but the sodium content should be maintained at a fairly low level. If the patient refuses to eat because the lack of sodium makes his food unpalatable, small amounts of sodium may be permitted while the progress of his clinical state is being continually watched. The tendency to overemphasize low-sodium content in the diets of patients with heart failure often results in development of hyponatremia or malnutrition and consequent weakness of the patient.

Diets should be adequate in vitamin-containing foods, including raw fruits and vegetables. If the patient is fairly well nourished before heart failure developed, it is not necessary to be too concerned about vitamin deficiency for avitaminosis is not likely to develop over a period of two to three days. If the patient exhibits evidences of malnutrition, then vitamins may be added to the diet accordingly

Water

Water should be permitted freely It is not necessary to force water; the beneficial results that might be obtained in some instances are usually offset by the nausea and vomiting and dyspepsia produced by large quantities of water If the patient's diet contains little sodium, it is unlikely that he will retain water Furthermore, his thirst will be reduced The patient should be allowed a choice of warm or cool

drinks. It would not be advisable, however that he use extremely cold water or drinks. A record should be kept of the intake and output of water which can be done as easily at home as in the hospital. Most patients and their relatives enjoy keeping an account of diet and water intake and output, and this is extremely valuable for determining the progress of the patient's disease. Later when the patient improves and can be moved about, he should be weighed regularly in order to ascertain the status of his edema.

Diuretics

Most patients with chronic congestive heart failure do not need diuretics. The current tendency to use mercurial diuretics as soon as congestive heart failure is suspected is not only unnecessary but may even produce fatalities. Diuretics should be reserved for those circumstances in which the foregoing measures fail to produce desired effects. Among the diuretics the mercurials are the most potent and most useful. There are several satisfactory preparations available.

Mercurial diuretics should never be administered intravenously except when it is absolutely necessary i.e., if the patient's failure is so far advanced that he has circulatory collapse or has such a sluggish circulation that a mercurial diuretic deposited in the muscle might not be absorbed and delivered to the kidneys and tissues of the body No immediate deaths have been reported following intramuscular or subcutaneous administration of a mercurial diuretic. These *routes of administration are therefore,* advocated as being safer; furthermore, the drug apparently is as potent clinically when administered intramuscularly as intravenously If there is a great deal of edema in the lower parts of

the body the mercurial diuretic should be injected into the deltoid muscles.

Only enough of the drug should be given to produce the desired effects In most instances either 0.5 or 1.0 cc. of Mercuhydrin intramuscularly will induce adequate diuresis. If diuresis is excessive, the patient may lose edema too rapidly dyspnea will rapidly subside and he may show considerable clinical improvement, but within 24 hours he may die in the state which resembles that of hyponatremia and has been reported to be similar to "shock." This little understood type of delayed death is extremely disturbing especially when the patient has shown improvement. It is therefore, dangerous to produce excessive diuresis. The patient's failure usually has developed slowly and there is no need to remove the edema too rapidly particularly since it may be dangerous If adequate diuresis is obtained with ½ to 1 cc., the dosage need not be increased However if this amount does not produce diuresis the next day or the day after it may be increased to 2 cc. If diuresis still does not occur then aminophylline may be administered intravenously or ammonium chloride may be given orally for several days prior to the next dose of the mercurial diuretic. The latter should be employed if hypochloremia exists. Hypochloremia will usually result in inadequate response to mercurial diuretics. A daily dose of 8 to 12 grams of ammonium chloride may be given orally for a day or two; then if a mercurial diuretic is readministered, diuresis will usually ensue. If adequate response is obtained with mercurial diuretics, then 0.3 to 0.5 cc. may be given daily until the patient's failure is fully compensated. Mercurial diuretics should not be used however if the other measures outlined previously produce adequate response.

Ammonium chloride should not be employed as enteric coated tablets, as many of them will not dissolve and will

therefore not produce the desired effects. Of course, they will not produce nausea and vomiting especially if they fail to be dissolved and absorbed, but neither will they have any pharmacologic action.

If the patient insists upon the inclusion of sodium chloride in his diet, the physician might continue the daily use of small doses of a mercurial diuretic in doses of 0.25 to 0.3 cc. in order to insure excretion of sodium chloride equal in amount to that taken in his diet.

Hyponatremia. It is important to bear in mind that if the patient is receiving mercurial diuretics, his diet is low in sodium and if he is also receiving ammonium chloride, a syndrome of hyponatremia is likely to develop. Physicians should be aware of this, for the hyponatremic syndrome is becoming more frequent with present day management of congestive heart failure. There is really no justification for permitting this syndrome to develop. It is only a manifestation of carelessness on the part of the physician. The syndrome of hyponatremia (8) consists of anorexia and occasional vomiting, skeletal muscle cramps, weakness, lethargy, depression of urinary volume and chlorides, and rapid gain in weight due to accumulation of edema fluid. The patient may appear on casual examination to be in shock, but his pulse is full and his blood pressure is maintained. He has difficulty breathing, and azotemia may develop. Examination of the blood will reveal the concentration of sodium and chloride to be low. When this occurs, an intravenous injection of 200 to 300 cc. of a 3 per cent solution of sodium chloride may be given in association with additional amounts (20 to 40 grams) orally until the concentrations of chloride and sodium in the blood return to within normal limits. The clinical picture will improve as the sodium levels in the blood serum rise. More detailed aspects of the mercurial diuretics will be discussed in Chapter Three.

General Hygienic Measures

During management of a patient with congestive heart failure, the usual nursing care should be carefully maintained. The patient's bowel function should be regulated. If he tends to become constipated, particularly if he has received morphine, only a mild laxative should be given, either milk of magnesia, mineral oil or cascara sagrada. If the patient has difficulty with use of a bed pan, it may be necessary to use an enema and as soon as possible allow him to use a commode placed next to his bed. During the early phases of his illness the nurse should not bathe the patient daily; as soon as he feels better he may be given a daily sponge bath in bed. He should not be annoyed with too vigorous therapy, too many drugs or unnecessary attention from nurses. Only essential procedures should be employed.

Other Procedures

Other procedures which may be beneficial in management of a patient with congestive heart failure include paracentesis for removal of pleural or peritoneal fluid. It is rather interesting how dramatic diuresis may be immediately after removal of large quantities of peritoneal fluid in some patients. Similarly, a patient with dyspnea will show considerable improvement with respiration following removal of pleural fluid, particularly if there is a great deal of shifting of the mediastinal structures. Cyanosis will subside quickly and discomfort from the fluid will disappear. Venous pressure may drop sharply and the patient may be on the road to rapid recovery. Paracentesis of the pleura or peritoneum should be done only when the fluid present is producing discomfort and may be repeated as frequently as necessary.

It seems advisable to administer penicillin routinely with the usual obvious clinical considerations, to all patients with congestive heart failure until compensation has been fully established. Eight hundred thousand to 1,000,000 units a day divided into two doses may be administered as a prophylactic measure, because with accumulation of fluid in the lungs there is a tendency for these patients to develop bronchial pneumonia. Penicillin may also reduce the possibility of abscess formation if a pulmonary infarct should develop from emboli. Certainly if an infarcted lung develops as a complication, penicillin therapy should be instituted immediately if it is not already in progress.

Phlebotomy should be used only in patients who do not respond to therapy and whose venous pressure is extremely high. Before this procedure is undertaken, the hemoglobin should be measured to make sure the patient is not suffering from severe anemia. If the patient has no anemia, then 500 cc. of blood may be withdrawn slowly Occasionally beneficial is so-called "bloodless" phlebotomy in which tourniquets are placed on the thighs, the pressure in the blood pressure cuff is raised to a level greater than diastolic but less than systolic pressure, and the circulation is intermittently released. However this is not as effective as removal of 500 cc. of blood. As a rule, patients with congestive heart failure are orthopneic and their legs are below heart level and fairly well distended with blood anyway Placing cuffs on the legs is discomforting and annoying to the patient and will not produce a great deal more benefit than filling of the veins in the already dependent parts of the body of an orthopneic patient. If anemia is not present, removal of 500 cc. of blood can be done easily and within a short period of time, permitting the patient to rest comfortably thereafter

Southey tubes may be employed in patients with severe edema who do not respond favorably to the usual measures

of therapy They are not often useful but when a patient is extremely edematous, several liters of blood may be re moved by this method.

Although *exchange resins* are being used increasingly to-day they are still in the phase of clinical investigation, since their value has not definitely been established. They may produce gastrointestinal disturbances and if proper ones are not used they may result in loss not only of the sodium ion but of other electrolytes, such as magnesium and potassium, as well. It is therefore not advisable to use these resins, especially since data obtained thus far indicate that they are of no great value in management of patients with congestive heart failure. If sodium elimination is necessary small doses of mercurial diuretics can accomplish more or surely the same amount of elimination of sodium with less disturbances to the patient.

Routine use of *anticoagulants* is not recommended in con gestive heart failure.

Ambulation

As the patient improves while in bed, he should be in structed to move around a bit in order to prevent his venous circulation from remaining sluggish and thus apparently avoid thromboembolic complications. By the time he is ready to become ambulatory sufficient strength of skeletal muscles has been developed so that ambulation will not be too difficult for him. When the patient has recovered sufficiently to permit him to get out of bed the physician should instruct him carefully regarding the manner in which this is best done It is important that he undertake the process gradually probably getting up for five or 10 min-utes each morning and afternoon on the first day for 10 minutes more the second day and so forth until he is finally

up most of the day Approximately two weeks should be required for the patient finally to be up and about again. It must be realized that such a patient has serious cardiac disease, his myocardium is weak, and the exertion associated with getting out of bed may be sufficient to produce acute cardiac failure. While the patient is becoming ambulatory the physician should watch his progress closely if he should fail to respond satisfactorily he should be returned to bed for another week or so Such caution will avoid serious accidents in association with ambulation of a previously seriously ill patient with congestive heart failure.

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(CHAPTER THREE)

Digitalis

BECAUSE digitalis is so important in the management of congestive heart failure, a clinical discussion of this drug seems appropriate. Since its introduction by Withering in 1785 digitalis has been employed extensively in the management of cardiac states including congestive heart failure. There have been numerous attempts to introduce drugs with digitalis like action, but none has yet supplanted it. Many substances have pharmacologic effects similar to digitalis, well known among which are Strophanthus, squill, Apocynum and barium. This large and ever-expanding group of drugs and their derivatives has been the source of considerable confusion among clinicians who find it difficult to acquaint themselves with all of these or to know which ones to select for use. Such difficulties, however can be obviated if it is realized that only a few preparations are necessary for the management of congestive heart failure. It is far wiser for the physician to become thoroughly acquainted with two or three preparations, use them routinely familiarize himself with their actions in all the various stages of congestive failure and its complicating clinical states and their various useful dosage schedules than it is to have a superficial knowledge of many different substances and preparations and thus apply them unsatis

factorily For example, a pure glycoside is employed for intravenous and oral administration during acute phases and the whole leaf for usual oral administration. The clinician should familiarize himself with a preparation which is excreted slowly like whole digitalis leaf or digitoxin, the latter a pure glycoside, and with a rapidly excreted preparation, like digoxin also a pure glycoside. A few such preparations will meet all of his needs. Certainly he should at least learn the therapeutic applications of whole leaf of digitalis and a pure glycoside for intravenous administration before employing other preparations (*Table I*)

ACTIVE PRINCIPLES

The preparations of digitalis are obtained from *two plants Digitalis purpurea* and *Digitalis lanata* (1 2) Preparations of the former are more commonly employed, consisting of *whole leaf* of digitalis and the pure glycoside, *digitoxin* which is a more purified form of the long employed digitaline crystallisee of Nativelle. *Gitoxin* and *gitalin* are other glycosides of *Digitalis purpurea*

From *Digitalis lanata* are derived *Lanatoside A*, *Lanatoside B*, *Lanatoside C* and *digoxin* the last two of which are most commonly employed.

(1) Powdered whole leaf Whenever digitalis whol leaf is ordered in a prescription, the whole leaf of *Digitalis purpurea* is dispensed by the pharmacist. The preparation contains not only the glycosides but other substances, most of which are unknown, as are their actions. This preparation is excreted relatively slowly requiring as long as three weeks in some patients. The powdered leaf is dispensed as pills capsules, tablets and tinctures, but rarely as infusions and suppositories. Each tablet, capsule, or pill contains 0.1 gram or 1½ grains or 1 international unit, unless otherwise

TABLE I

CER AIN DIGITALIS PREPARATIONS AND RELATED DRUGS

Preparation	Origin	Description	Use
Digitalis (whole leaf)	D. purpurea L.	Dried leaves, tablet, pill ...	
Digitoxin	D		
Dosi			

maintenance daily—4.8 USP units

... let 0.8 USP unit/ tablet

A dose 0.4–0.8 USP unit t.i.d.

therapeutically desirable constituents of digitalis

Solution.— .0 USP unit/cc. 0.5 USP unit/cc. Tablet — USP unit

Essentially as for Digilan

ILURE

Preparations	Origin	Description	Unit	Dose
Gitalin (amorphous)	D. purpurea L.	Glycoside	*Tablets.* 0.25 mg./tablet	For full digitalization 4–6.5 mg. total. 2–3 tablets daily for 3 4 days Then 0.25–0.75 mg. daily
Digoxin	D lanata Ehrh.	) Solution in 70% alcohol) Tablet	. mg. = USP unit	LV (see text) Oral 0.5 mg. (gr / 120)
Digilanide	D. lanata Ehrh.	Lanatoside A 47% Lanatoside B 16% Lanatoside C 37%	*Sol Heav.* 0.2 mg/cc. 0.33 mg./cc. *Tablet* 33 mg.	2–4 tablets daily until digitalized Then tablets daily (see text)
Lanatoside C	D. lanata Ehrh.	Pure glycoside, Digilanide C	*Solution* 0.2 mg/ c. 33 mg./cc *Tablet* 33 mg	tablets daily until digitalized Then 1– tablets daily (see text)
*Ouabain	Strophanthus gratus	G strophanthin	Soln. ouabain ampules mg in 0. c. 0.5 mg in .0 cc	5 mg LV or I.M. (see text)

TABLE I (*Continued*)

Preparation	Origin	*Description*	*Unit*	Dose
Strophanthus	S. kombé S. hispidus	Dried ripe seed	Gm. = 55 mg. USP Reference ouabain	60 mg. (gr)
Strophanthus tincture	S. kombé S. hispidus	Alcohol solution of active principles	cc. = 55 mg. USP Reference ouabain	0.5 c. (minims 8)
Strophanthin	S kombé	Glycoside	mg. = 0.5 mg. USP Reference ouabain	0.5 mg. (gr / 10)
Scillaren	Urginea maritima	parts Scillaren A part Scillaren B	*Solution.*— cc. = 0.8 mg. *Tablets.*— 0.8 mg.	.4 mg. 3 4 times daily Then 0.8 mg. 2–4 times daily
Scillaren B	Urginea maritima	Amorphous Scillaren B	*Solution.*— 0.5 mg. cc. ampules	0.5 mg. I.V. once in 24 hrs
Squill fluid extract	Urginea maritima	Hydro-alcoholic percolate		cc. (½ minims)

These are the only preparations with which the physician need be familiar. He will usually use digitalis (whole leaf) and only one pure glycoside for parenteral administration.

specifically ordered by the physician. The tincture, a 10 *per cent alcoholic solution* of whole leaf is still used extensively Because it deteriorates rapidly it should *not be employed* unless there is a special reason for its use and then only if the preparation is fresh, i.e., if it has not been on the shelf of the pharmacy or patient's home more than three months and has been well stoppered.

Dose The digitalizing dose of powdered whole leaf for an adult is *approximately* 1.2 to 2.0 grams and for the tincture 12 to 20 cc. The method of administration has been discussed previously under the management of congestive heart failure (Chapter Two) Only about one fifth of whole digitalis leaf is absorbed through the gastrointestinal tract and one to two units is excreted daily

(2) Digitoxin. Like the powdered whole leaf this relatively pure glycoside of *Digitalis purpurea* is long-acting. It is almost completely absorbed from the gastrointestinal tract when administered orally but since it is a pure preparation, it is employed intravenously also Its action is said to be essentially the same as the powdered whole leaf but this has been disputed by some. Its toxic manifestations are the same. Apparently it produces nausea and vomiting not by direct gastric irritation but by its effect on the central nervous system. Digitoxin is not rapidly acting beginning to act about one hour after intravenous administration and reaching a maximum in about four hours. As in the case of the whole leaf a period of two to three weeks is required for it to be excreted. This slow rate of elimination should be taken into consideration when digitoxin or powdered whole leaf is employed.

Dose The single intravenous dose varies from 1.2 to 2.0 milligrams, the average patient requiring 1.2 milligrams. The maintenance dose varies from 0.05 to 0.3 milligram (average 0.2 milligram) The same dose is employed for oral adminis-

tration and the schedule is the same as that described for powdered whole leaf It is well to remember that 0.1 gram powdered whole leaf and 0.1 milligram digitoxin represent 1 biologic unit; thus, digitoxin is 1000 *times* more potent than the powdered whole leaf

(3) Digoxin. Digoxin is a pure crystalline glycoside of the leaf of *Digitalis lanata*. It appears to have the same pharmacologic effects as powdered whole leaf of *Digitalis purpurea* and digitoxin but differs from these two preparations in that it is *rapidly acting* and *rapidly eliminated* a full digitalizing dose being excreted in 48 hours. Its pharmacologic and toxic effects are relatively brief Its chief use in cardiology is in instances of uncertainty about the need for digitalization and in cases of previous recent digitalis intake. Because it is relatively insoluble in water it is dispensed in alcohol for intravenous administration and the dose is diluted with normal saline before it is administered

Dose The digitalizing dose varies from 2.0 to 5.0 milligrams the average being about 3 5 milligrams. The daily maintenance dose varying from 0.5 to 0.75 milligram is relatively large, due to the rapid rate of elimination.

(4) Lanatoside C. This is a crystalline glycoside of *Digitalis lanata* which has essentially the same pharmacologic characteristics as digitoxin It is the most rapidly acting and most rapidly eliminated of the preparations of digitalis employed today Its effect begins within 10 minutes to two hours after intravenous administration but is short lived lasting six to 36 hours, and it is excreted within three to six days. Its actions appear to be the same as powdered whole leaf of *Digitalis purpurea*.

Dose The digitalizing oral dose varies from 5.0 to 10.0 milligrams (average 7 5 milligrams) the maintenance oral dose from 1.0 to 1 5 milligrams The intravenous single dose varies from 0.8 to 1 6 milligrams, and the maintenance in

travenous dose is about 0.4 milligram every six hours. Details of administration have been discussed previously

(5) Ouabain. Although ouabain is not a preparation of digitalis, it is employed frequently enough to warrant its discussion briefly A glycoside of *Strophanthus gratus* it is usually employed in America for emergency purposes only because of its extremely rapid action. Its maximal effect occurs within 30 minutes to two hours after administration and lasts 24 to 72 hours. Because it is rapidly eliminated, digitalis preparations are used for maintenance. *Strophanthus kombé* is the source of other glycosides.

The most rapidly acting preparation is acetyl strophanthin, which attains its maximal effect within 10 minutes. Various K strophanthins are available but will not be discussed here.

Dose The average digitalizing intravenous dose of ouabain is 0.8 to 1.0 milligram. The initial intravenous dose is 0.5 milligram followed by 0.1 milligram intravenously every 30 to 60 minutes until the desired effects are obtained.

ACTION

(1) Cardiac muscle. (a) *Irritability* The myocardium is made more irritable, that is, the muscle responds more readily to stimulation. Its *threshold* to stimulation is reduced so that the myocardium becomes more prone to develop ectopic beats, tachycardias, such as auricular flutter and fibrillation, paroxysmal tachycardias, and ventricular fibrillation. Such disturbances in cardiac mechanism are manifestations of digitalis intoxication or overdigitalization which are of value in the clinical use of the digitalis preparations.

Increased irritability of the myocardium results in improvement of cardiac function whenever the myocardium

becomes less responsive to stimulation and is "sluggish," as occurs with myocardial degeneration. This improvement in responsiveness to stimulation is conducive to improved myocardial function, provided the irritability does not become excessive. When irritability is increased to such a degree that premature contractions and more serious disturbances in mechanism occur cardiac function becomes impaired.

(b) *Contractility* This phenomenon is increased by digitalis, as manifested by augmented *myocardial tone* The *systolic shortening* is prolonged and accentuated resulting in more complete emptying of the heart. The *diastolic tone* is also increased, as evidenced by a tendency for the muscle to relax less during diastole. The greater *force* of contraction enables the myocardium to do more work. Visscher and his associates (3 4) have shown digitalis to increase cardiac efficiency i.e., there is a greater percentage of useful work from energy expended.

These actions are obviously of definite benefit to a failing heart. The prolongation of the diastolic phase of the cardiac cycle may be detrimental in aortic valvular insufficiency because more time becomes available for leakage of blood back into the left ventricle from the aorta. Except for this factor the actions on myocardial contraction are to produce improvement of cardiac function as a pump

(c) *Slowing of cardiac rate* Digitalis retards the cardiac rate primarily by its action on the vagus nerve but the precise mechanism of this action remains obscure. Apparently it acts by way of the carotid sinus reflex, by means of changes in blood pressure, by chemical stimulation of the carotid sinus, and by increasing the sensitivity of the myocardium and sino-auricular node to vagal impulses. Digitalis also directly depresses the sino-auricular node and conduction tissue, including the atrioventricular node. The

vagal action has been established by showing in experimental animals and man that the slowing of the cardiac rate by digitalis is almost completely abolished by vagotomy or atropine.

That congestive heart failure is associated with an increase in cardiac rate or sinus tachycardia is well known, but the exact method by which this occurs has not yet been ascertained. With improvement of cardiac function by digitalis, the mechanisms responsible for the increase in cardiac rate are altered so that it declines toward normal. It has been suggested that venous hypertension activates the Bainbridge reflex. With administration of digitalis and appearance of cardiac compensation, venous pressure definitely declines, and if the Bainbridge reflex were partially responsible for the increased cardiac rate, the rate should also decrease.

The cardiac slowing in *auricular fibrillation* is due to depression of the atrioventricular node, which results in blocking of the supernumerary auricular and especially weak impulses that reach the A V node. The ventricles therefore, are stimulated less frequently and the cardiac rate decreases. Furthermore retardation of the ventricular rate increases the time allowed for ventricular filling and, with an increase in the force of contraction as a result of digitalis therapy stroke volume is increased and, in turn, cardiac output.

(2) Action on the circulation. (a) *Arterial blood pressure* in man may increase decrease, or remain unchanged. A rise in blood pressure is due in part to an increase in stroke volume, an increase in the force of ventricular contraction and possibly an increase in arteriolar tone.

(b) *Venous pressure* declines with cardiac compensation consequent to digitalis action. McMichael and Sharpey Schafer (5) thought this was due to direct action of digitalis

on veins reducing their tone As indicated in Chapter One when venous pressure rises venous tone or "tightness" of fit of the venous wall upon the blood within must be increased Digitalis may reduce venous pressure by decreasing this tightness of fit. Eichna and associates (6) presented data which showed that digoxin reduces venous tone or produces venous relaxation. The venous action of digitalis apparently is extremely important in the mechanism for improvement of cardiac function in congestive heart failure.

(c) *Circulation* time is reduced by digitalis as cardiac function and the rate of circulation of blood through the tissues improve

(d) If *circulating blood volume* is increased, although it probably is elevated only slightly if at all, during congestive failure, it diminishes following administration of digitalis. The mechanism and temporal aspects of this response are not known. Apparently it is associated with the reduction in edema and increased volume of extracellular fluid accompanying congestive failure.

(e) *The volume of cardiac output is equal to venous return of blood* during failure and after compensation. Obviously therefore if cardiac output is increased by digitalis and this increase is maintained for any length of time venous return must be equally increased by digitalis.

(3) Cardiac size. By increasing cardiac tone, digitalis diminishes cardiac size Cohn and associates (7) showed, by means of teleoroentgenograms, that the size of the cardiac shadow is reduced by digitalis. This has been contested by some observers, but it is now generally agreed that reduction in cardiac size occurs because digitalis increases the amount of contraction of the myocardial fibers during systole and reduces lengthening during diastole

(4) Central nervous system. Nausea and vomiting produced by digitalis apparently originate from its action on

the medullary portion of the brain. The vagal, vasomotor and respiratory centers appear to be affected by digitalis. The delayed nausea and vomiting produced by the drug through its central action must be differentiated from the immediate nausea and vomiting which result from local gastric irritation following oral administration of the drug. With toxic quantities of digitalis, psychosis and green or yellow vision may occur Such reactions do not reflect toxic cardiac effects or overdosage from the cardiac point of view

(5) Renal action. There is no irrefutable evidence to support direct renal action as the responsible factor in diuresis. In fact, the process by which digitalis produces an increase in urinary volume, or diuresis, is unknown. It is generally believed that diuresis which follows administration of digitalis to a patient with congestive heart failure is due to improvement of the circulation through the kidneys. Improvement in the pumping function of the heart is thought to be accompanied by more satisfactory renal circulation, with improvement in glomerular filtration and reduction in tubular reabsorption. There is no adequate evidence to establish a role of humoral or hormonal factors in the diuresis, even though existing knowledge of renal function would strongly implicate such factors. The data concerning the diuresis are too meager however to explain the mechanism.

INDICATIONS

Although digitalis may be indicated in other states, such as auricular flutter and auricular fibrillation (especially in the presence of a rapid ventricular rate a marked pulse deficit and congestive heart failure) and paroxysmal supraventricular (auricular and nodal) tachycardia, the present discussion will treat its use in congestive heart failure only

It will become evident that the principles of administration are similar for any of these indications

(1) Congestive Heart Failure. Digitalis should be employed in the management of congestive heart failure, regardless of the cause or type of the disease. It is particularly beneficial in patients who have cardiac hypertrophy due to extra work by the ventricle, such as heart disease with congestive failure as a result of arterial hypertension or aortic stenosis. Congestive failure due to acute myocarditis responds poorly if at all, to digitalis, even when large doses are administered. The same tends to be true for heart disease caused by hyperthyroidism, myxedema malnutrition, or severe anemia. Obviously it is more important to remove the etiologic factor in these cases, when this is possible, than to treat the failure itself

Congestive failure in the presence of auricular fibrillation or flutter can be expected to respond most dramatically to digitalization, since the disturbance in cardiac rhythm usually contributes to the development of failure. Improvement of the cardiac mechanism and of the myocardial contraction will naturally lead to compensation The drug should be used for the failure, even though auricular fibrillation is associated with a slow ventricular rate

Digitalis is of limited value if the failure is due to certain mechanical factors creating disturbances in the cardiac output independent of the force of ventricular contraction. Concretio cordis or any cause of serious interference with ventricular filling extreme stenosis of the mitral or aortic valves or extreme coarctation of the aorta would fall into this category

(2) Myocardial Infarction. The drug should be used with *caution* and *special care* in certain disease states. Since *myocardial infarction predisposes to serious mechanisms of* ventricular origin, such as tachycardia or fibrillation and since

digitalis, through its tendency to produce myocardial irritability may create these disturbances, this drug should be employed only when necessary Certainly it is not indicated when failure is mild and compensation can be obtained with bed rest, oxygen, salt restriction and mercurial diuretics. When failure is obviously progressing however and other measures fail, then the drug should be used.

(3) Conduction disturbances. It is true that digitalis tends to depress the conduction tissue and therefore should not be used for congestive heart failure if other measures produce adequate control. When the failure continues or is progressively worsening, then the drug should be administered slowly and cautiously The response should be carefully observed in order to avoid overdigitalization.

(4) Shock. That digitalis is contraindicated in the presence of peripheral circulatory collapse or shock, in association with surgical and medical causative factors, is well known. Although it is not known how digitalis aggravates peripheral circulatory collapse, it is probably related to a venodilative action of the drug.

(5) Prophylactic use of digitalis. Although many physicians employ the drug prophylactically to prevent the development of congestive failure, this is not to be recommended. For example, the preoperative use of digitalis prophylactically although popular cannot be justified on the basis of evidence available. On the contrary operative and postoperative shock may even be aggravated by the drug. Furthermore, the practice of administering almost fully digitalizing doses preoperatively with the idea that then only a small quantity need be given should failure develop is to be condemned. It is just as simple, if not easier to digitalize fully a patient free of digitalis than one who has previously received inadequate quantities of the drug. Obviously

whenever failure develops digitalization should be rapidly achieved.

DOSAGE

The dosage schedules advocated for the various commonly employed digitalis preparations have been briefly mentioned previously The common difficulty encountered in general practice is that of administering the proper dose of digitalis to achieve the desired results. When a physician is not familiar with digitalis he hesitates to employ it. Furthermore, it is not generally remembered that digitalis *cannot* be administered by any specific dosage rule. Unlike most drugs with no special pharmacologic action digitalis does not produce its effects through psychogenic or placebo actions, and definite beneficial results are obtained only when adequate digitalizing quantities are given Physicians who employ a given dosage routine in prescribing drugs will not find such a plan satisfactory for digitalis.

The proper dose of digitalis for a given patient with congestive heart failure is the amount necessary to produce the desired effects. In fact, this is a good rule to follow for any drug The amount of digitalis necessary will vary from patient to patient and, therefore, no definite and general dosage schedule is applicable to all. Only when digitalization has been achieved can it be known that the proper dosage has been attained Since it is possible to ascertain the attainment of digitalization only from the clinical response, the physician must be able to recognize the manifestations of digitalization. Certain general rules, however have been found safe and dependable for achieving satisfactory digitalization.

Standardization of digitalis has created much difficulty and discussion. Regardless of the methods employed the *ultimate factor* for standardization is clinical experience

with sick people. Satisfactory results may be obtained within fairly wide variations in potency for a given digitalis preparation. The main requirements are: (1) that the potency of a given preparation not be altered appreciably as would occur if it deteriorated and became impotent with time and (2) that standard preparations vary within prescribed limits so that some general dependability in potency might be insured among all commercially available preparations.

After considerable effort by representatives of many disciples of medicine the world over the standard selected for the United States is the USP unit. *One USP unit* is contained in 0.1 gram powdered digitalis leaf regardless of its form of preparation—tablet, capsule, pill or tincture For example, since a tincture is a 10 per cent alcoholic solution, 0.1 gram powdered leaf (1 USP unit) would be found in 1 cc. of the tincture. These preparations are assayed by the manufacturers against a *USP reference standard* The pure glycosides like digitoxin, digoxin, and Lanatoside C are about 1000 times more potent than the powdered whole leaf; therefore, 0.1 milligram possesses the potency of 0.1 gram whole leaf or 1 USP unit. With a knowledge of the biologic potency in terms of USP units and the weight of the preparation, the physician should have no difficulty obtaining *adequate* digitalization of his patient.

Powdered whole leaf The average quantity of digitalis required to produce digitalization is about 1 USP unit per eight to 10 pounds of body weight. Some allowance should be made for edema and for fat in obese patients. This is merely a guide and not a guarantee that the patient will be digitalized when that precise amount has been administered

Whenever a patient can take digitalis by mouth and no emergency exists necessitating immediate digitalization by the intravenous route oral administration of the whole leaf is the method of choice.

Slow oral digitalization. It is preferable to digitalize the patient slowly while he is confined in bed but not necessarily hospitalized. In any person with congestive heart failure requiring digitalis there is sufficient impairment of cardiac function to require bed rest, at least until a cardiac inventory justifies a different approach. The patient may be given 1 or 2 units (1 or 2 tablets of 0.1 gram, or 1½ grains, each of whole leaf) three times daily An allowance is made for the loss of one unit per day which is sufficiently accurate since digitalization is determined by clinical response and not by any precise quantity of drug administered. For example about 20 units of digitalis would be required to obtain digitalization in a patient weighing 160 pounds. If one unit is given three times daily about 10 days will be needed to accomplish full digitalization. As the estimated dose is approached, the physician should see the patient frequently and should be notified if anything unusual develops such as nausea, vomiting or palpitation. This dosage schedule should be continued until digitalization is attained even if the estimated digitalizing dose must be exceeded The maintenance dose will vary the average being 1 to 2 units (1 to 2 tablets of 0.1 gram or 1½ grains each) daily The physician must be alert to subtle overdigitalization or loss of that state of medication when the patient is receiving his maintenance dose.

Rapid oral digitalization. (a) *Powdered whole leaf* The Eggleston method of administration is satisfactory for rapid oral digitalization. One half of the estimated digitalizing dose is given immediately one half of the remaining dose six to eight hours later and then 2 units every six to eight hours until full digitalization is obtained If 20 units is the estimated dose, 10 tablets of 1 unit (0.1 gram) each should be given immediately 5 tablets six to eight hours later and 2

tablets every six to eight hours until desired physiologic effects are produced. Thereafter the daily maintenance dose of 1 or 2 tablets is given.

(b) *Digitoxin* A single digitalizing dose is about 1 2 milligrams given slowly as a single intravenous injection. Some patients require 2 0 milligrams and must therefore be given an additional quantity of 0.2 to 0.4 milligram at six to eight hour intervals until the desired effects are obtained. The daily maintenance dose is about 0.2 milligram. It is possible to switch to 0.1 or 0.2 gram whole leaf orally for maintenance.

(c) *Digoxin* The average rapidly digitalizing dose is 3 5 milligrams (range 2.0–5 0 milligrams) given intravenously over a period of 24 hours Because this pure glycoside is so rapidly eliminated the daily maintenance dose is about 0.5 milligram. It is preferable to dilute the alcoholic preparation of digoxin before intravenous administration.

(d) *Lanatoside C.* The average dose is 1 2 milligrams (range 0.8–1.6 milligrams) given in a single intravenous injection. It is more effective, however to administer a single dose of 0.8 to 1 2 milligrams initially and then 0.2 to 0.4 milligram at four hour intervals until digitalization is attained. The maintenance intravenous dose is 0.4 milligram every 6 hours.

The average oral dose of Lanatoside C is 7 5 milligrams (5.0–10.0 milligrams) given in divided doses in a period of 24 hours. The maintenance dose is 1.0 to 5 milligrams daily This glycoside is excreted moderately rapidly

(e) *Ouabain and strophanthus* The average digitalizing dose of *ouabain* a strophanthin, is 0.5 to 1.0 milligram d ministered intravenously Preferably an initial dose of 0.5 milligram should be given, followed by 0.1 milligram t 30 to 60 minute intervals until the desired effects are obtained.

MANIFESTATIONS OF DIGITALIZATION

The initial sign of satisfactory digitalization is *general improvement* of the patient. He is more interested in his surroundings, more alert mentally and physically, and has the appearance of being less acutely ill. *Dyspnea* begins to subside, the *cardiac rate* declines, the *pulse* becomes fuller and stronger, *diuresis* begins, the *edema* begins to subside, and the *veins in the neck* become less distended. These signs of improvement develop progressively. Digitalization should be continued after they appear, a shift to a maintenance dose being made only when the foregoing manifestations of improvement reach a maximum. At times it is necessary to ensure attainment of the maximal beneficial effects by continuing digitalization until the initial signs of intoxication or overdigitalization appear. This stage may be recognized by the fact that digitalis appears to be producing no definite benefit and the other therapeutic measures employed in congestive failure likewise seem to be inefficacious. In most instances, however, intentional slight overdigitalization is not necessary.

In general, it is advisable to reduce the cardiac rate to 70 or 80 beats per minute. This usually occurs as compensation develops if sinus tachycardia is due to the failure. If the tachycardia is due to other causes, such as infections, or if there is associated myocarditis, the cardiac rate will not likely decline to the seventies. In the presence of auricular fibrillation, the ventricular rate should be reduced *to 70 to 80* beats per minute for best results.

MAINTENANCE OF DIGITALIZATION

Maintenance of adequate digitalization is known to exist by maintenance of the state of compensation, evidenced by

continued improvement. The patient remains free from edema, venous hypertension, and dyspnea. His cardiac rate at rest continues at 70 to 80 beats per minute, and the patient feels well. This state can usually be maintained by administration of 1 to 2 units daily. It is important to remember that a slow subtle accumulation of digitalis may occur with consequent eventual overdigitalization or that a slow subtle loss may result in escape from the digitalized state. If these phenomena are carefully considered on each visit to the patient, the maintenance dose may be either diminished or increased promptly to cope with the existing situation.

MANIFESTATIONS OF OVERDIGITALIZATION

The manifestations of overdigitalization may be divided into two main groups (1) gastrointestinal and (2) cardiac.

(1) Gastrointestinal. The earliest gastrointestinal manifestations of digitalis intoxication are anorexia, nausea, and vomiting, in that order. Anorexia may precede nausea and vomiting for several days, the latter two appearing as the intoxication progresses. The severity of these symptoms varies directly with the degree of intoxication.

Certain aspects of these gastrointestinal symptoms deserve special consideration to avoid confusion in therapy. *Firstly* it is necessary to remember that congestive heart failure is, in itself, often associated with gastrointestinal disturbances. The physician must, therefore, be able to distinguish the dyspepsia existing prior to digitalization from any new symptoms that might have been produced by digitalis and not by the congestive heart failure.

Secondly the gastrointestinal manifestations of digitalis intoxication appear to originate in the central nervous system and, therefore, would not be expected to develop until about four hours after administration of an oral dose of

whole leaf of digitalis Whenever nausea and vomiting occur immediately after the patient has swallowed a dose of digitalis, the symptoms originate from local action of the drug upon the gastric mucosa or psychic factors and are not due to general digitalis intoxication. Of course, toxic effects of digitalis may be manifested by nausea and vomiting within a few minutes after an intravenous injection of digitalis For proper digitalization, immediate and delayed gastrointestinal disturbances must be properly evaluated.

Thirdly the gastrointestinal manifestations of overdigitalization do not occur until the patient is almost digitalized, which is about the time he has received all the calculated digitalizing amount They should not be expected after only a small portion of the calculated dose has been administered. When overdigitalization becomes apparent, administration of the drug should be discontinued until the gastrointestinal disturbances disappear The patient may then be placed on the maintenance dose.

(2) Cardiac. The cardiac manifestations of overdigitalization constitute the most important signs of digitalis intoxication Of these premature contractions are the earliest and aside from gastrointestinal disturbances, occur more frequently than any other manifestation. Occasional at first, they increase in frequency as the intoxication progresses. *Bigeminy* or *coupling* appears later With more severe intoxication, *multiple* and *multifocal premature contractions* develop These are serious and are premonitory signs of paroxysmal tachycardia auricular flutter auricular fibrillation, ventricular tachycardia and finally ventricular fibrillation. Various degrees of heart block may develop the earliest of which is incomplete AV block, evidenced by prolongation of the P R interval. With advanced intoxication, this may progress to partial AV block, 2:1 block, or even complete block. Bundle branch block may also occur

Pulsus alternans, interference dissociation and excessive slowing of the cardiac rate (sinus bradycardia) are other cardiac manifestations of overdigitalization.

All these manifestations of disturbances in cardiac mechanism, with the exception of premature contractions, are of serious nature and should be avoided by careful digitalization. Most of the cardiac manifestations of overdigitalization are detectable at the bedside and all of them can be identified precisely by means of the electrocardiogram a method to be employed freely when doubt exists.

(3) *Other toxic manifestations.* There are many other manifestations of digitalis intoxication which are less common but which must be kept in mind. *Headache* is a common disturbance. Scotomata, blurring of vision, green or yellow vision, mental cloudiness, excitement or even toxic psychosis, and neuralgia involving various areas of the body have all been described.

Thrombosis and embolism, eosinophilia and allergic reactions have been attributed to digitalis but are not necessarily indicative of overdigitalization. Degenerative and focal necrotic changes in the myocardium have been described, but these are more prone to occur in the presence of myocarditis or acute and severe myocardial degeneration.

The changes produced in the electrocardiogram as well as other toxic manifestations will not be presented here, since they are too numerous to permit adequate discussion.

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(CHAPTER FOUR)

Mercurial Diuretics

MERCURY is one of the oldest and most widely used drugs in medicine. Its therapeutic applications have been varied, as indicated in the abundant literature on the subject. As early as the sixteenth century inorganic mercury was employed as a diuretic agent, but because its prolonged administration produced stomatitis, it fell into disuse until the early twentieth century when Zeiler introduced an organic mercurial compound Novasurol (the double salt of sodium mercurichlorphenyl oxyacetate with diethyl barbituric acid) for the treatment of syphilis. Its value as a diuretic agent was accidentally discovered by Saxl and Heilig (1) in 1920. Since then a succession of less toxic compound have been introduced, including Salyrgan® (sodium [O(hydroxy mercuric methoxyl propyl-carbamyl) phenoxy] acetate) Mercupurin® (Mercuzanthin sodium trimethyl-cyclopentane-dicarbonic acid methoxy-mercury-allylamide theophylline) Mercuhydrin® (sodium salt of methoxyoximercuripropylsuccinylurea with theophylline) and Thiomerin® [disodium salt of N(γ-carboxy-methyl mercaptomercuri-β-methoxy) propyl camphoramine acid] (mercaptomerin sodium) These and other new mercurial diuretics contain about the same amount of mercury: Salyrgan and Mercuzanthin, 37–42 per cent mercury by weight Mercuhydrin 39 milligrams per cc. and Thiomerin, 40 milligrams per cc.

CHEMICAL PROPERTIES

The pharmacologic effects of mercury depend upon the chemical constitution of the compound Thus, since local action is determined by the concentration of the mercurial ion, highly ionized inorganic compounds will produce greater toxic effects on tissues than will the less ionizable organic mercurial compounds (2) The rate of absorption and, therefore, the activity of the various compounds vary with their solubility being greater in aqueous solutions con taining large quantities of protein than in those with low concentrations. The chemical media within the body in the presence of therapeutic amounts of mercury thus affect solubility ionization and diffusion, which, in turn, influence the pharmacologic action of the mercury

The chemical forms which the mercury of a mercurial diuretic assumes after injection into the body are not known. The binding of mercury to proteins has been demon strated *in vitro* and *in vivo* but, of course, mercury may exist in some other combinations as well. The ionization equilibrium of protein mercurial complexes in the body is likewise unknown. Rates of diffusion are certainly influenced by binding of mercury to large protein molecules, and alterations in diffusion affect some of the physiologic re sponses of the body to injection of mercury It has been shown that under chemical conditions which exist in the body diffusion of mercury may be enhanced The strong affinity of mercury and other heavy metals for thiol groups has been demonstrated, but it has not been established that the action of mercury in the body is definitely mediated through reactions with thiol-containing compounds.

The mercurial ion is the active principle in all mercurial diuretics The diuretic action is essentially similar for ioniz

ble inorganic mercury organic mercurials and colloidal mercury but their toxicity differs considerably The rate, duration and amount of diuresis vary from one compound to another The highly ionizable compounds exert a more potent diuretic effect, per unit weight of mercury than do the organic compounds.

PHARMACODYNAMICS

The methods presently available for chemical analysis of mercury are relatively insensitive, and for this reason it has been difficult to study the metabolism of mercury within the body Because most of these technics require digestion of organic materials in the presence of reducing agents, large amounts of mercury may thus be lost through volatilization.

Absorption. Absorption of mercury may occur by way of the respiratory and gastrointestinal tracts, the skin, vagina, and subcutaneous tissues. The parenteral route of administration is more dependable than the oral or rectal, since absorption of mercury by the latter two routes is unpredictable. Mercury is rapidly absorbed after intramuscular injection, particularly in the presence of Theophylline. Without Theophylline (1 3-dimethylxanthine) however absorption of *Mercuparin* and Salyrgan is much slower Edematous or adipose tissue may reduce the rate of absorption considerably and may produce irritation at the site of injection. Absorption of Thiomerin from subcutaneous tissue appears to be satisfactory and its absorption from muscle is essentially the same as for Mercuzanthin and Salyrgan. Absorption is slow from ascitic fluid.

Studies of transfer of radiomercury of a labeled mercurial diuretic across a blister membrane revealed reduction in transfer by protein binding of the mercury The mercury was absorbed more slowly when suspended in a protein

medium. The rate of absorption or transfer did not differ for normal controls and for subjects with congestive heart failure and was not altered when the venous pressure was elevated by inflating a cuff around the arm (3)

Distribution. The form of mercurial compound, route and duration of administration determine the manner in which mercury is distributed throughout the body Mercurial poisoning sometimes occurs as a result of "overloading" or injury of the potential excretory processes. Renal insufficiency for example, influences the level of mercurial concentration in the tissues.

The excretion, distribution and storage of mercury in the body after a long course of inunction treatments differs from that observed after the single injection usually given for its diuretic effect. With inunction, the body achieves a state of "saturation" by frequent small doses, mercury becomes stored throughout the body and excretion reaches a maximum at two to three weeks and may continue for 60 days or more after administration has been discontinued (4) Following oral administration of a mercurial diuretic over a period of four days, there may be continued excretion in the urine for 16 additional days (5) Such observations indicate that mercury is stored in the body

No "state of saturation" is attained by the body following a single intravenous injection, nor is equilibrium of distribution achieved if renal function is normal. Excretion is so rapid that the observed regression of mercury in the blood is attributable largely to renal excretion. Some storage may occur after intravenous injection, but it is relatively small by comparison with that following inunction treatments of syphilis, in which about 50 per cent of the administered mercury may be stored.

Mercury is widely distributed in the body having been found in almost every organ, including bone. Its concentra-

tion is greatest in the kidney and next greatest in the liver Maximal concentration in the bile is delayed many hours after the peak concentration in the blood has been reached. After continuous administration, as by inunction, concentration in the bile may be higher than in the blood, but after a single intravenous injection, the relative concentration depends entirely upon the time of sampling Thus, if sampling were made 24 hours after injection, when concentration in the blood is low concentration in the bile might be higher This would not, however be true in the hours immediately following the injection.

After a single intravenous injection of a mercurial diuretic labeled with radioactive mercury this element was found to enter ascitic, pleural and edema fluid and sputum slowly None was found in sweat, gastric juice or spinal fluid. Washed human red blood cells contained no mercury After intravenous administration of labeled Mercuhydrin (6) the fecal content of mercury varied widely from 0.01 to 16 per cent.

Immediately after intravenous administration of a mercurial diuretic, there is a rapid reduction in concentration of mercury in the blood. In the presence of renal failure, however it remains elevated, and the distribution of mercury throughout the body differs from that observed when renal function is normal. Normally a large unidirectional shift of mercury into the urine occurs so rapidly that little time is available for the relatively slowly diffusing mercury protein complex to reach equilibrium of distribution throughout the body If the kidneys fail to excrete the mercury equilibrium of distribution may be attained. The extracellular fluid compartment in states of generalized edema may serve as a large storage depot for mercury

The form in which mercury is stored in the body is unknown but it is thought by some to be in combination with

tissue proteins. This "stored" mercury may remain in the body for varying lengths of time. Like the storage of lead certain chemical environments, such as a high pH encourage deposition of mercury whereas acid precursors favor mobilization from storage depots The concentration of mercury in the blood may be modified by factors which affect storage equilibrium

Excretion. Mercury is excreted from the body primarily in the urine but may also appear in the feces by way of the saliva bile and intestinal mucosa. In the presence of renal insufficiency or "overloading," the fecal route assumes greater importance

The manner in which mercury is excreted depends upon several factors, including the route and duration of administration and the rate of absorption. When mercury is administered slowly to the point of saturation, there is a gradual increase in excretion up to a maximum at the end of two to three weeks. The quantity eliminated is determined by the dosage administered and the concentration of mercury attained in the blood. The "saturation point" of the blood is reported to be 3 milligrams per liter (7); excretion begins when this level is exceeded. Because of large storage depots in the body mercury may continue to be eliminated for as long as six months after cessation of therapy

The most rapid excretion of mercury occurs within several minutes after intravenous or intramuscular injection. The rate and completeness of excretion of the various diuretics are essentially the same With normal renal function urinary excretion of intravenously administered mercury has been found to be complete in 24 to as long as 72 hours. Excretion of the last 10 to 20 per cent occurs so slowly that the complete time course of urinary excretion is difficult to establish by the relatively insensitive chemical methods available for analysis of mercury

The time course of excretion of mercury in urine following oral administration of a diuretic labeled with radiomercury has been described by Overman and associates (8). This involves the variable of intestinal absorption, but maximal urinary excretion of mercury was attained approximately 200 minutes after ingestion. Of the mercury recovered in the urine, about 50 per cent was recovered during the first 400 minutes after administration of the capsules, the last 20 per cent having been recovered between 600 and 1500 minutes after ingestion. Urinary excretion has been noted for 16 days after oral administration for four days.

Studies have revealed a qualitative directional similarity for practically all the curves of urinary volume, excretion of mercury and concentration of mercury for a variety of mercurial compounds, organic and inorganic. Excretion became maximal in 1 to 2 hours after injection and then descended as a parabolic curve. Curves for mean urinary excretion after intravenous injection were almost identical for many of the mercurial compounds. Whereas diuresis following intramuscular injection was not perceptibly slower than following intravenous injection, excretion of mercury was less rapid.

The time course of renal excretion has been studied by means of a mercurial diuretic labeled with radiomercury (9, 10). Following intravenous injection the mercury appeared at the tip of ureteral catheter in three and one-half to five minutes, but concentration was not maximal until about 20 minutes after injection. The lag in time between renal excretion and extraction of mercury from the serum reflects retention within the kidney. The rate of excretion is less rapid in subjects with congestive heart failure than in normal subjects and is even slower still in those with renal insufficiency, tending to vary indirectly with the degree of renal failure. The time required for one-half of all the ad

ministered mercury to be excreted in the urine serves as an index of the differences among normal and diseased subjects. In normal subjects half the mercury administered either intravenously or intramuscularly is excreted in approximately two hours, but some mercury is usually still present in the urine at the end of 24 hours. In some subjects with congestive heart failure more than twice as long is required for excretion of one-half the administered mercury the time varying considerably with the state of the failure. Renal insufficiency may be accompanied by extremely delayed excretion of mercury In one subject only 19 per cent was excreted in eight days, although there was a large volume of hyposthenuric urine during this time. Excretion cannot therefore be assumed to be complete in 24 hours simply because the volume of urinary output is large. Daily administration may result in an accumulation of mercury in the body of normal subjects and an even greater accumulation in the presence of disease states, such as congestive heart failure and renal insufficiency

The chemical state in which mercury is excreted is unknown. It may be excreted in different chemical forms in the stool and urine, and these forms may vary with time by either of these avenues of excretion, depending in part upon the chemical state of the urine or feces at the time. The extent to which the excreted mercurial compound may be influenced by the chemical state in which it is administered such as the bichloride, succinate salicylate colloidal mercury or the organic mercurial diuretics, has not been determined nor has it been definitely established that mercury is excreted as the same compound in which it was administered.

Site and mode of action. Whether or not mercury possesses extrarenal actions which influence diuresis has not been established with certainty Findings of hemodilution ob-

tained by refractometric and blood chemical studies would seem to suggest extrarenal action. However no evidence has been found of mobilization of fluids with consequent hemodilution before mercurial diuresis occurs. That renal action alone should be associated with hemodilution is difficult to comprehend, since water and electrolytes should not enter the circulation any more rapidly than they are released by the kidneys, were renal excretion and renal action entirely responsible for their migration.

Extensive studies of the renal effects of mercurial diuretics suggest that mercury acts solely as a result of its effect on the kidney. Small amounts of mercury injected into a single renal artery resulted in diuresis from that kidney only (18). When the doses of mercury were increased, there was diuresis from the opposite kidney as well. Apparently the extracting capacity of the injected kidney was exceeded, and the additional mercury moved into the other kidney through the blood stream. The observations by Govaerts (11) who removed a kidney from an animal during maximal mercurial diuresis and transplanted it into the neck of an untreated animal, where the diuresis continued, corroborate the renal action of mercury. Nevertheless, there may also be extra renal effects, such as increased blood pressure which may affect mercurial diuresis.

The mechanism and site of action of mercury have been the subject of some investigation but are still not completely understood. The rate of glomerular filtration is apparently not increased by mercurial diuretics alone. It may rise slightly when a mercurial diuretic is given in combination with a xanthine, but not sufficiently to explain the diuresis. The rate of glomerular filtration may even fall if extremely large doses of a mercurial diuretic are administered.

The possibility of a tubular site of action is suggested by increased urinary excretion of electrolytes and water in the

absence of any detectable variation in their concentration within the blood or any appreciable change in rate of glomerular filtration. Mercury was observed by Richards (12) to abrogate the ability of the renal tubules to reabsorb and selectively retain diffusable substances. It has been conjectured that the repeated observation by investigators of decreased tubular reabsorption with consequent increased urinary excretion of electrolytes and water may be explained on the basis of changes in enzymatic processes in the tubular cells concerned with transport and selective reabsorption of electrolytes. It has been shown that certain enzymatic systems may be inactivated by mercury and reactivated by BAL.

Studies of specific renal functions which have been made during mercurial diuresis include glucose T_m, glomerular filtration, renal PAH extraction and renal clearances of mannitol, sodium, chloride and uric acid. Results suggest that mercury reduces specific proximal tubular function and glucose reabsorption in man. Data obtained for animals have differed from those for man and, because renal function varies among different animals, correlation and interpretation of such data must be performed cautiously.

The distal tubule has been suggested by Duggan and Pitts (13, 14) as the site of action of mercurial diuresis. Dogs receiving a saline injection before and after injection of mercury exhibited increased excretion of sodium with increased doses of mercury to a certain level, after which larger amounts of mercury failed to have any effect. Maximal sodium diuresis was attained more rapidly with larger doses. On the basis of this upper level of sodium excretion, it would seem that renal tubular reabsorptive function is only partially "mercury sensitive," estimated at about 15 per cent of that reabsorbed during the control periods. This value would agree with the view that 80 to 85 per cent is reabsorbed

in mercury insensitive proximal tubules The fact that there was no greater excretion of sodium with mercury in combination with pitressin than with mercury alone led to the conclusion that the site of action was the same for both: the distal segment. These investigators further concluded that only when the amount of mercury administered is large enough to damage the tissues was sodium reabsorption in the proximal tubules influenced by the mercury

These studies, however do not unequivocally establish the distal tubule as the only site of action of mercury in man. The experiments were performed on dogs receiving large quantities of physiologic normal saline solutions and large doses of mercury Furthermore, the differentiation of therapeutic and toxic levels of mercury is difficult to establish, and the conclusions are further subject to cautious acceptance because they are based on rather broad assumptions.

The most impressive response to mercurial injections is the diuresis which follows. Although it is usually complete in 24 hours it may continue for 48 hours. Urinary excretion varies from 1 to 3 liters but in the presence of anasarca, 15 liters of urine have been excreted by some patients. Throughout diuresis, the specific gravity of the urine is depressed.

The preceding outpouring of electrolytes in the urine is even more spectacular than the water diuresis. There is definitely increased excretion of chloride, sodium, potassium and magnesium but not particularly of phosphates and sulfates. The excretion of electrolytes is determined by the concentration of sodium and chlorid in the body hyponatremia and hypochloremia being associated with slight or no diuretic effect. Excessive excretion of sodium, chloride potassium and water is generally followed by reduced output of these elements for about one to three days or

until restitution of normal water and electrolyte balance

When large quantities of electrolytes and water are excreted the blood undergoes certain chemical alterations There is usually a fall in concentration of chloride in serum and extracellular fluid and an elevation in concentration of bicarbonate the concentration of sodium remaining fairly constant (15)

A greater negative balance of chloride than of sodium was observed by Schwartz and Wallace (15) Potassium appeared in the urine in greater concentration than could be explained on the basis of its concentration in the extracellular fluid. Additional observations are required to define these effects more precisely especially for potassium.

Since the diuretic response to injection of mercury is affected by the electrolyte concentration in the body it may be influenced by premedication with acidifying salts. Anything which enhances renal blood flow and rate of glomerular filtration such as bed rest and administration of xanthines, may accentuate the diuretic response.

Many physiologic responses to the intravenous injection of a mercurial diuretic occur besides excretion of sodium and water Blood pressure may increase occasionally because of generalized vasoconstriction. The volumes of the limbs and of the kidney have been observed to decrease, accompanied by a transient decline in renal blood flow with resultant transient antidiuretic effect (16) Changes of hemoconcentration and hemodilution are inconstant. Blood urea is not unidirectionally altered it may rise fall or remain unchanged.

TOXICITY

Because mercury is a protoplasmic poison, its toxicity is in direct proportion to its degree of ionization At the site

of contact with the tissues, mercury will produce a local irritation. Orally administered mercury may be associated with nausea, vomiting abdominal distress, and diarrhea. The application of suppositories may produce proctitis and ulceration. Intramuscular or intravenous administration is associated with local reaction at the site of injection, which may be slightly diminished by xanthines and more so by thiol groups.

Mercurial action is widespread throughout the body but certain organs seem to have a greater affinity for it. Necrotic changes in the tubular epithelium of the kidney occur as a result of the administration of large quantities of mercury and in animals they may appear when smaller doses are given for prolonged periods. The possibility of injuring the renal tubular epithelium by prolonged frequent injections of therapeutic amounts of mercury seems remote since renal function tests and histologic examination of the kidneys have revealed no apparent injury to patients receiving sufficient quantities to effect diuresis. Intravenous injection of the usual doses of mercury may be followed, on occasion, by renal tubular damage. The liver may undergo toxic changes when large quant ties of mercury are given.

The reaction to mercury varies among different species of animals. For example doses adequate to establish diuresis in man have been observed to cause transient or permanent renal damage in animal experiments. When mercury and albumin were administered simultaneously in rats, proteinu ria resulting from injection of a foreign albumin intensified the toxic effect of the mercury on the renal tubules. Protein given prior to the injection of mercury has a protective effect. It is not known what importance these observations have from a clinical point of view

Of greater clinical significance are the toxic effects of intravenous injections of mercurial diuretics on the cardio-

vascular system. These vary with the dosage of mercury administered Glutathione, cysteine and BAL may be given to prevent generalized vasoconstriction and other more dangerous reactions (16)

A disturbance in cardiac mechanism is frequently encountered as a manifestation of mercurial toxicity The cardiotoxic effects of mercury vary considerably in different animals In the turtle, for example, heart block developed following administration of dilutions of either organic or inorganic preparations of mercury of 1:100,000 or greater; sodium thiosulfate reversed this action (17) Monothiols, cysteine and glutathione and dithiol BAL had an inhibiting effect on the 50 per cent lethal dose in cats dogs and mice (16 18) These compounds reversed heart failure produced in a heart lung preparation by infusions of Salyrgan. Blood pressure fell rapidly when large doses of mercury were given. The occurrence of ventricular fibrillation was successfully reduced in dogs by administration of magnesium sulfate along with the mercurial diuretic (19)

The combination of magnesium sulfate with a mercurial diuretic was observed by Pines and coworkers (19) to reduce the frequency of ventricular fibrillation in dogs but had no effect on disturbances in conduction. In the presence of anoxia, the cardiac muscle is more susceptible to the toxic effect of mercury Quinidine apparently has a precipitating rather than an inhibiting effect insofar as ventricular fibrillation is concerned. An overdose of Mercuhydrin has been reported to have produced ventricular asystole and subsequently death, and Mercurophylline and Mersalyl have been known to bring on ventricular fibrillation.

Fatalities reported following the intravenous injection of mercurial diuretics indicate the severity of toxic cardiovascular reactions. When death ensues, it usually occurs within one to three minutes after injury has occurred. The

rate of injection influences these reactions when the injection is made rapidly the concentration of mercury "perfusing" the heart may be so high as to bring about a fatal cardiac disturbance, whereas slow injection will permit adequate mixing with the blood and yield a relatively low concentration of the mercury Deaths have occurred not only following a first injection but unexpectedly after many previously well tolerated injections as well. In some instances there were antecedent warning signs apprehension, dyspnea, substernal pain, sweating, pallor changes in pulse, and giddiness. Nonfatal convulsions have also occasionally occurred. Fever chills asthmatic attacks and cutaneous eruptions and other delayed reactions have been encountered as well. There have been a disproportionately large number of deaths in children the dosage of mercury used for patients in this age group seems much too large for the body weight.

When any true reaction, immediate or delayed, develops, additional mercurials should be employed only with extreme caution. Despite the fact that following the occurrence of delayed reactions, the injection of a different mercurial diuretic is occasionally well tolerated, it is advisable to employ subsequent mercurial diuretics cautiously whenever an immediate or delayed reaction occurs. When their continued administration seems absolutely essential, a small dose of a different preparation should be given by a route other than the intravenous, and if this is satisfactorily tolerated the dose may be increased.

The most commonly used diuretics, i.e., Mercuzanthin, Salyrgan and Mercuhydrin, all of which contain theophylline, seem to have about the same toxic properties. Local reactions at the site of injection differ however by the intramuscular and subcutaneous routes. The cardiotoxic properties of mercurial diuretics may be inhibited, without reducing the diuretic effect, by the simultaneous use of

monothiol compounds. For example the cardiotoxic and local reactions of Thiomerin, in which theophylline is replaced by sodium mercaptoacetal, are minimal, whereas its diuretic potency is equivalent to other diuretics (20) Its toxicity seems greater however in other respects.

In rats for example, more delayed deaths occurred within five to seven minutes after injection of Thiomerin than with the use of Mercuhydrin or Mercurophylline administered intravenously or subcutaneously (21) Furthermore, delayed toxic effects observed over a period of four days after injection of Thiomerin were essentially equivalent to those encountered with Mercuhydrin Mercuzanthin and Salyrgan. Diarrhea and stomatitis occurred more frequently in the dogs following administration of Thiomerin than with the other organic mercurials These observations in animals indicate that the reported low toxicity of this new drug requires further study before it can be accepted

APPLICATIONS

The use of diuretics in congestive heart failure is not mandatory In fact, it is not necessary in most cases and may even precipitate death when used injudiciously Only when the usual therapeutic procedures i.e., bed rest, administration of oxygen, digitalis and morphine, prove to be ineffective in eliminating the accumulation of extracellular fluid and maintaining it at a desirable level should one resort to diuretics

The most potent and most useful diuretics are the mercurial diuretics. The relative efficacy of the various preparations available commercially will not be discussed here When administered intravenously all seem to produce approximately the same amount of diuresis Subcutaneous injection of Thiomerin or Mercuhydrin has been shown to re

sult in diuresis equal in amount to that obtained following intramuscular or intravenous administration of other preparations. Because this route obviates office visits and is attended by fewer side reactions, it has particular practical advantage in the management of patients with congestive heart failure.

Since no immediate deaths have been reported following administration of the drugs by either the intramuscular or subcutaneous routes, they are advocated as the routes of choice. Furthermore, the intramuscularly administered drug is as effective therapeutically as that given intravenously. If the lower parts of the body are extremely edematous, the drug should be injected into the deltoid muscle. The intravenous route should never be employed unless absolutely necessary: if the patient is in circulatory collapse or if his circulation is so sluggish that a mercurial diuretic injected into the muscle might not be absorbed and delivered to the kidneys and tissues of the body, then the intravenous route would have to be used.

Suppositories containing mercurial diuretics have been found to be impractical because of local irritation and unpredictable absorption. Because the potency of the drug is limited when administered orally, the relatively large quantity necessary to produce diuresis is usually accompanied by nausea, vomiting and diarrhea, and this route is therefore unsatisfactory in the early management of severe congestive heart failure. It may be useful for administering maintenance doses of the drug to keep the patient "dry" after satisfactory diuresis has been accomplished by means of the parenteral route.

Like the oral route, the subcutaneous route eliminates the necessity for office visits. Olson (22) has suggested that 0.25 to 0.33 cc. Thiomerin or Mercuhydrin administered subcutaneously daily by the patient or a relative may be

effective economical and simple. Although these small amounts may produce no apparent diuresis, the subtle changes produced by frequent injections will maintain desired weight levels satisfactorily Large amounts may be needed in severely decompensated patients. The proper dosage in individual cases may be ascertained readily by clinical trial. For patients who insist on using a little sodium in their diets, daily use of 0.25–0.3 cc. of the diuretic subcutaneously at home will insure excretion of sodium chloride equal in amount to intake in most, but not all, patients. This procedure must be tried to ascertain its value in any given patient.

The proper dose of the drug is the smallest amount which will produce the desired effects in a given patient. Usually 0.5 or 1 cc Mercuhydrin intramuscularly will induce adequate diuresis. The recent practice of administering 2 cc. daily in the initial therapy of congestive heart failure is usually unnecessary and may prove harmful. Aside from the toxic effects of accumulation of mercury more serious disturbances in electrolyte and water balance may result from excessive diuresis. The clinical state of the patient should dictate the rate of reduction in extracellular fluid the amount of mercury which will cause a daily loss of two to three pounds of weight in the edematous patient is usually adequate and should be considered maximal for safety When the symptoms and signs of accumulation of extracellular fluid have subsided, maintenance at this level should be attempted No benefit can be obtained by forcing additional diuresis beyond this maximal response and deleterious effects may develop as a result of depletion of electrolytes and water Excessive diuresis may cause the patient to lose edema too rapidly Even though dyspnea may rapidly subside and considerable clinical improvement may become manifest, patients have been seen to die within 24 hours in

a state of hyponatremia and apparent "shock." This little understood type of fatality clearly illustrates the dangers of excessive diuresis.

If 0.5 to 1 cc. of a mercurial diuretic fails to produce adequate diuresis, the dose may be increased the next day to 2 cc. If this is likewise ineffective, aminophylline or theophylline, 0.5 gram, may be administered intravenously along with the mercurial diuretic, or ammonium chloride may be given orally for several days prior to the next dose of the mercurial diuretic. The latter should be employed in the presence of hypochloremia, which is usually associated with inadequate response to mercurial diuretics. A daily dose of 8 to 12 grams ammonium chloride given orally for a day or two when followed by readministration of a mercurial diuretic, will usually increase diuresis considerably. Enteric coated tablets of ammonium chloride should not be employed, since many of them will fail to dissolve and will therefore not produce the desired effects. Of course, they will not be accompanied by nausea and vomiting, especially if they do not dissolve and become absorbed but for the same reason neither will they have any beneficial pharmacologic effect. If adequate response is obtained then 0.3 to 0.5 cc. of the mercurial diuretic may be given daily until the patient's failure has been fully compensated. Rest in bed will improve renal blood flow in the patient with congestive heart failure and it is therefore important for the patient in severe congestive heart failure.

The performance of phlebotomy with removal of 500 to 750 cc. of blood, just preceding injection of mercury may be followed by satisfactory diuresis when previously administered mercurial diuretics have been ineffective. The most common causes for inadequate diuretic response to mercurials are renal failure or a disturbance in electrolyte metabolism. When the latter is present, it should of course,

be corrected before the mercurials are tried again. In some instances removal of ascitic or of pleural fluid will result in a response to the mercurial diuretics which had failed previously. This is especially true in the presence of severe ascites and pleural effusion.

It should be pointed out that the underlying fundamental cardiac state, and not the time element, should be the guiding factor in the treatment of congestive heart failure. Although mercurial diuresis will improve certain signs and symptoms of the clinical syndrome, such as edema, the disappearance of these manifestations does not necessarily denote complete restitution of cardiac function. Whereas the proper use of mercurial diuretics is helpful in the treatment of congestive heart failure, they should not be considered as substitutes for digitalis nor as a specific cure for cardiac disease. In fact, when used injudiciously, they may have harmful effects.

Trial and error will determine the proper maintenance dosage of mercury. Smaller, more frequent amounts are preferable to larger doses at less frequent intervals. Weight should be maintained at a level below which symptoms appear, to avoid the accumulation of fluid and the error of producing excessive diuresis with frequent large doses. Even in the same patient it may be necessary to alter the maintenance dose from time to time. A change in the amount of salt ingested, disturbances in cardiac mechanism, occurrence of infections, and other factors may necessitate an increase in the maintenance dose.

Under present day management of congestive heart failure, the syndrome of hyponatremia is occurring with increasing frequency. The physician should be aware of this syndrome, since it reflects negligence on his part. Manifestations of the syndrome include anorexia and occasional vomiting, skeletal muscle cramps, weakness, lethargy, de

pression of urinary volume and chlorides, and rapid gain in weight due to accumulation of edema fluid. Casual examination may suggest a state of shock, but the patient's pulse will be full and his blood pressure will be maintained. Breathing is difficult, and azotemia may develop Examination of the blood plasma will reveal low concentrations of sodium and chloride. To correct this condition, an intravenous injection of 200 to 300 cc. of a 3 per cent solution of sodium chloride may be given in association with additional amounts (20 to 40 grams) orally until the concentrations of chloride and sodium in the blood return to within normal limits. The clinical picture will improve as the sodium levels in the blood serum rise.

CONTRAINDICATIONS

Mercurial diuretics should not be used in the presence of acute renal disease, such as acute glomerulonephritis or chronic renal disease with insufficiency Whereas blood urea nitrogen may be elevated in patients with congestive heart failure without any primary renal disease, it is nevertheless wise to use mercurial diuretics with extreme caution, if at all, when the blood urea nitrogen exceeds 60 milligrams per 100 cc. Likewise, continued administration of a mercurial diuretic is contraindicated in the presence of albuminuria, hematuria or oliguria appearing only after administration of a mercurial diuretic.

When a patient fails to respond favorably to previous injections of mercurial diuretics, further use of the drug should be discontinued until the patient's entire clinical state including the kidneys, has been carefully studied and any disturbance in electrolytes has been corrected. Any immediate reaction to an intravenous injection of a mercurial diuretic is likewise contraindication for further use of mer

cury at least by this route Tachycardia, faintness, pallor sweatiness and asthmatic attacks are among the immediate reactions which should be *regarded as warning signs* delayed manifestations include fever chills and cutaneous rashes. A different preparation administered by another *route is occasionally tolerated by the patient.*

If tetany develops from excessive loss of calcium during diuresis, no additional mercury should be employed until *this has been corrected. Excessive diuresis may lead to digitalis intoxication,* and the administration of mercurial diuretics should be discontinued until the surplus digitalis *has been excreted Mercurial therapy need not be discon*tinued because of minor reactions, such as cramps in the legs, but during further administration the dosage or fre*quency of injection should be reduced after the chloride and* sodium levels in the blood plasma have been measured

Because the intravenous route has been associated with *most of the reported dangerous reactions, the intramuscular* or subsequent routes are advocated for routine administration, the intravenous route being employed only when circulatory impairment may inhibit satisfactory therapeutic response by other avenues.

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Index

A

B

C

D

This Book

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By George E. Burch, M.D F.A.C.P

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